

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
13 December 2001 (13.12.2001)

PCT

(10) International Publication Number
WO 01/94346 A1

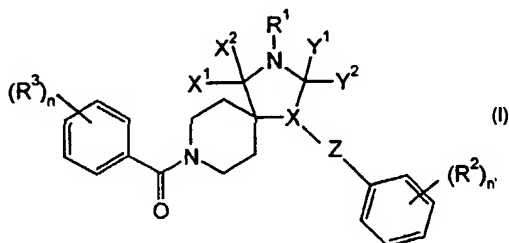
- (51) International Patent Classification⁷: C07D 471/10, A61K 31/445 // (C07D 471/10, 239:00, 221:00) (74) Agent: POPPE, Regina; Grenzacherstrasse 124, CH-4070 Basle (CH).
- (21) International Application Number: PCT/EP01/06305 (81) Designated States (*national*): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CO, CU, CZ, DE, DK, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW.
- (22) International Filing Date: 1 June 2001 (01.06.2001)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 00112285.2 8 June 2000 (08.06.2000) EP (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- (71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH]; 124 Grenzacherstrasse, CH-4070 Basle (CH).
- (72) Inventors: GALLEY, Guido; Katzenbuckelweg 14, 79618 Rheinfelden (DE). GODEL, Thierry; Mittlere Strasse 7, CH-4056 Basle (CH). GOERGLER, Annick; Mittlerer Sennweg 13, F-68000 Colmar (FR). HOFFMANN, Torsten; Kleinhueninger Strasse 15, 79576 Weil am Rhein (DE). KOLCZEWSKI, Sabine; Schillerstrasse 35, 79618 Rheinfelden (DE). ROEVER, Stephan; Schlossstrasse 15, 79594 Inzlingen (DE).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 1,3,8-TRIAZA-SPIRO'4,5!DECAN-4-ONE DERIVATIVES AS NEUROKININ RECEPTOR ANTAGONISTS



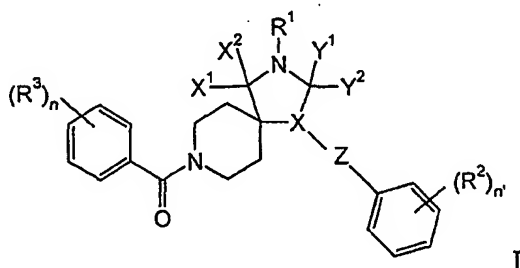
(57) Abstract: The invention relates to compounds of the formula (I) wherein R¹ is hydrogen, lower alkyl, lower alkenyl, phenyl or the following groups -(CH₂)_m-non aromatic heterocyclyl, which is optionally substituted by lower alkyl, or is -(CH₂)_m-heteroaryl, which is optionally substituted by one or two substituents selected from the group consisting of lower alkyl, lower alkoxy, halogen, CF₃, benzyl or cyano, or is -(CH₂)_m-C(O)-NRR', -(CH₂)_m-C(O)-lower alkyl, -(CH₂)_m-C(O)-O-lower alkyl, -(CH₂)_m-O-lower alkyl, -(CH₂)_m-CH[C(O)-O-lower alkyl]₂, -(CH₂)_m-CH(OH)-CH₂-O-phenyl, -(CH₂)_m-CH(CF₃)OH, -(CH₂)_m-OH, -(CH₂)_m-CN, -(CH₂)_m-NRR',

-(CH₂)_m-cycloalkyl or -(CH₂)_m-CHF₂; R² is hydrogen, lower alkyl, halogen or lower alkoxy; R³ is lower alkyl, lower alkoxy, halogen or CF₃; R, R' are the same or different and are hydrogen or lower alkyl; X is > N-, > C = or > CH-; X¹/X² are independently from each other hydrogen, hydroxy or lower alkoxy or may be together an oxo group; Y¹/Y² are independently from each other hydrogen, lower alkyl, -(CH₂)_n-phenyl or may be together an oxo group; Z is a bond, -CH₂- or -C(O)-; m is 0, 1, 2, 3 or 4; n is 2 or 3; n' 0, 1 or 2; and pharmaceutically acceptable acid addition salts thereof. The described compounds have a good affinity to the NK1 receptor.

WO 01/94346 A1

1,3,8-TRIAZA-SPIRO[4,5]DECAN-4-ONE DERIVATIVES AS NEUROKININ RECEPTOR ANTAGONISTS

The present invention relates to compounds of the general formula



wherein

- 5 R^1 is hydrogen, lower alkyl, lower alkenyl, phenyl or the following groups
 $-(CH_2)_m$ -non aromatic heterocyclyl, which is optionally substituted by lower alkyl, or is
 $-(CH_2)_m$ -heteroaryl, which is optionally substituted by one or two substituents selected from the group consisting of lower alkyl, lower alkoxy, halogen, CF_3 ,
 10 benzyl or cyano, or is
 $-(CH_2)_m-C(O)-NRR'$,
 $-(CH_2)_m-C(O)$ -lower alkyl,
 $-(CH_2)_m-C(O)-O$ -lower alkyl,
 $-(CH_2)_m-O$ -lower alkyl,
 15 $-(CH_2)_m-CH[C(O)-O$ -lower alkyl] $_2$,
 $-(CH_2)_mCH(OH)-CH_2-O$ -phenyl,
 $-(CH_2)_m-CH(CF_3)OH$,
 $-(CH_2)_m-OH$,
 $-(CH_2)_m-CN$,
 20 $-(CH_2)_m-NRR'$,
 $-(CH_2)_m$ -cycloalkyl or
 $-(CH_2)_m-CHF_2$;

R^2 is hydrogen, lower alkyl, halogen or lower alkoxy;

R^3 is lower alkyl, lower alkoxy, halogen or CF_3 ;

- 2 -

- R,R' are the same or different and are hydrogen or lower alkyl;
- X is >N-, >C= or >CH-;
- X¹/X² are independently from each other hydrogen, hydroxy or lower alkoxy or may be together an oxo group;
- 5 Y¹/Y² are independently from each other hydrogen, lower alkyl, -(CH₂)_m-phenyl or may be together an oxo group;
- Z is a bond, -CH₂- or -C(O)-;
- m is 0, 1, 2, 3 or 4;
- n is 2 or 3;
- 10 n' 0, 1 or 2;

and to pharmaceutically acceptable acid addition salts thereof.

The compounds of formula I and their salts are characterized by valuable therapeutic properties. It has been surprisingly found that the compounds of the present invention are antagonists of the Neurokinin 1 (NK-1, substance P) receptor. Substance P is a naturally
15 occurring undecapeptide belonging to the tachykinin family of peptides, the latter being so-named because of their prompt contractile action on extravascular smooth muscle tissue. The receptor for substance P is a member of the superfamily of G protein-coupled receptors.

The neuropeptide receptor for substance P (NK-1) is widely distributed throughout
20 the mammalian nervous system (especially brain and spinal ganglia), the circulatory system and peripheral tissues (especially the duodenum and jejunum) and are involved in regulating a number of diverse biological processes.

The central and peripheral actions of the mammalian tachykinin substance P have been associated with numerous inflammatory conditions including migraine, rheumatoid
25 arthritis, asthma, and inflammatory bowel disease as well as mediation of the emetic reflex and the modulation of central nervous system (CNS) disorders such as Parkinson's disease (Neurosci. Res., 1996, 7, 187-214), anxiety (Can. J. Phys., 1997, 75, 612-621) and depression (Science, 1998, 281, 1640-1645).

Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially
30 migraine, Alzheimer's disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and

other respiratory diseases including allergic rhinitis, inflammatory diseases of the gut including ulcerative colitis and Crohn's disease, ocular injury and ocular inflammatory diseases reviewed in "Tachykinin Receptor and Tachykinin Receptor Antagonists", J. Auton. Pharmacol., 13, 23-93, 1993.

- 5 The usefulness of neurokinin 1 receptor antagonists for the treatment of certain forms of urinary incontinence is further described in "Neuropeptides, 32(1), 1-49, (1998)" and "Eur. J. Pharmacol., 383(3), 297-303, (1999)".

Furthermore, Neurokinin 1 receptor antagonists are being developed for the treatment of a number of physiological disorders associated with an excess or imbalance of
10 tachykinin, in particular substance P. Examples of conditions in which substance P has been implicated include disorders of the central nervous system such as anxiety, depression and psychosis (WO 95/16679, WO 95/18124 and WO 95/23798).

The neurokinin-1 receptor antagonists are further useful for the treatment of motion sickness and for treatment induced vomiting.

- 15 In addition, in The New England Journal of Medicine, Vol. 340, No. 3 190-195, 1999 has been described the reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist.

Furthermore, US 5,972,938 describes a method for treating a psychoimmunologic or a psychosomatic disorder by administration of a tachykinin receptor, such as NK-1
20 receptor antagonist.

NK1 receptor antagonists have been reported to have also a beneficial effect in the therapy of traumatic brain injury (oral disclosure by Prof. Nimmo at the International Tachykinin Conference 2000 in La Grande Motte, France, October 17-20, 2000 with the title "Neurokinin 1 (NK-1) Receptor Antagonists Improve the Neurological Outcome
25 Following Traumatic Brain Injury" (Authors: A.J. Nimmo, C.J. Bennett, X.Hu, I. Cernak, R. Vink)."

Objects of the present invention are the compounds of formula I and pharmaceutically acceptable salts thereof, the preparation of the above-mentioned compounds, medicaments containing them and their manufacture as well as the use of the above-
30 mentioned compounds in the control or prevention of illnesses, especially of illnesses and disorders of the kind referred to earlier or in the manufacture of corresponding medicaments.

The compounds of formula I can also be used in form of their prodrugs. Examples are esters, N-oxides, phosphate esters, glycoamide esters, glyceride conjugates and the like. The prodrugs may add to the value of the present compounds advantages in absorption, pharmacokinetics in distribution and transport to the brain.

5 The most preferred indications in accordance with the present invention are those, which include disorders of the central nervous system, for example the treatment or prevention of certain depressive disorders or emesis by the administration of NK-1 receptor antagonists. A major depressive episode has been defined as being a period of at least two weeks during which, for most of the day and nearly every day, there is either
10 depressed mood or the loss of interest or pleasure in all, or nearly all activities.

The following definitions of the general terms used in the present description apply irrespective of whether the terms in question appear alone or in combination.

As used herein, the term "lower alkyl" denotes a saturated straight- or branched-chain alkyl group containing from 1-7 carbon atoms, for example, methyl, ethyl, propyl,
15 isopropyl, n-butyl, i-butyl, t-butyl and the like.
Preferred lower alkyl groups are groups with 1-4 carbon atoms.

As used herein, the term "lower alkenyl" denotes a unsaturated straight- or branched-chain alkyl group containing from 2-7 carbon atoms, for example, ethenyl, propenyl, isopropenyl, n-butenyl, i-butenyl, t-butenyl and the like.
20 Preferred lower alkyl groups are groups with 2-4 carbon atoms.

The term "lower alkoxy" denotes a group wherein the alkyl residues are as defined above, and which is attached via an oxygen atom.

The term "halogen" denotes chlorine, iodine, fluorine and bromine.

The term "cycloalkyl" denotes a saturated carbocyclic group, containing 3-6 carbon
25 atoms.

The term "non aromatic heterocyclyl" denotes, for example, pyrrolidinyl, 5-oxo-pyrrolidinyl, 2-oxa-oxazolidinyl, piperidyl, piperazinyl, morpholinyl, imidazolidinyl or pyrazolidinyl. Preferred groups are pyrrolidinyl, 5-oxo-pyrrolidinyl, 2-oxa-oxazolidinyl, piperidyl, piperazinyl or morpholinyl.

30 The term "heteroaryl" denotes, for example pyridinyl, 1,3,5-triazinyl, pyrimidinyl, quinoxalinyl, pyrazinyl, isoxazolyl, benzoimidazolyl, 1,2,4-oxadiazolyl, triazolyl, tetrazolyl, thiazolyl, thienyl, furyl, pyranyl, pyrrolyl, imidazolyl, pyrazolyl, isothiazolyl, piperazinyl or piperidyl. Preferred groups are pyridinyl, 1,3,5-triazinyl, pyrimidinyl, quinoxalinyl,

pyrazinyl, imidazolyl, thiazolyl, isoxazolyl, benzoimidazolyl, 1,2,4-oxadiazolyl, furyl and thienyl.

The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, 5 phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulfonic acid, p-toluenesulfonic acid and the like.

Preferred are all compounds, wherein R^3 is trifluoromethyl and n is 2.

Exemplary preferred are compounds, in which X is >N-, X^1/X^2 are together an oxo group and Y^1/Y^2 are both hydrogen, for example the following compounds:

10 8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(4,6-dimethoxy-[1,3,5]triazin-2-yl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one,

8-(3,5-bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-3-(4,6-dimethoxy-[1,3,5]triazin-2-yl)-1,3,8-triaza-spiro[4.5]decan-4-one,

15 8-(3,5-bis-trifluoromethyl-benzoyl)-3-pyridin-3-yl-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one,

8-(3,5-bis-trifluoromethyl-benzoyl)-3-(2-isopropylamino-ethyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one,

8-(3,5-bis-trifluoromethyl-benzoyl)-3-(2-pyrrolidin-1-yl-ethyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one,

20 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-3-pyridin-4-yl-1,3,8-triaza-spiro[4.5]decan-4-one,

8-(3,5-bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-3-methyl-1,3,8-triaza-spiro[4.5]decan-4-one,

25 8-(3,5-bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-3-(3-dimethylamino-propyl)-1,3,8-triaza-spiro[4.5]decan-4-one,

8-(3,5-bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-3-pyridin-4-yl-1,3,8-triaza-spiro[4.5]decan-4-one and

8-(3,5-bis-trifluoromethyl-benzoyl)-3-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one.

Further preferred are compounds, in which X is >N-, X¹/X² are together an oxo group and one of Y¹/Y² is hydrogen and the other is different from hydrogen.

Examples of such compounds are:

- (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-1-phenyl-1,3,8-triaza-
5 spiro[4.5]decan-4-one,
- (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one,
- (rac)-2-benzyl-8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one,
- 10 (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-phenyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one,
- (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-1-phenyl-3-pyridin-3-yl-methyl-1,3,8-triaza-spiro[4.5]decan-4-one,
- (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2,3-dimethyl-1-phenyl-1,3,8-triaza-
15 spiro[4.5]decan-4-one,
- (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-1-phenyl-3-(2-pyrrolidin-1-yl-ethyl)-1,3,8-triaza-spiro[4.5]decan-4-one,
- (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-3-(3-dimethylamino-propyl)-2-methyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one,
- 20 (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2,3-dimethyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one,
- (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-3-(2-piperazin-1-yl-ethyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one,
- (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-3-(2-pyrrolidin-1-yl-ethyl)-1-o-tolyl-
25 1,3,8-triaza-spiro[4.5]decan-4-one,
- (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-3-(2-piperidin-1-yl-ethyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one,
- (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-3-(2-methoxy-ethyl)-2-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one,

(rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-3-(2-morpholin-4-yl-ethyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one and

(rac)-8-(3,5-dichloro-benzoyl)-2-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one.

Preferred are further compounds, wherein X is >N-, X^1/X^2 and Y^1/Y^2 are oxo groups,
5 for example the following compounds:

8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione,

8-(3,5-bis-trifluoromethyl-benzoyl)-3-pyridin-3-yl-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione,

3-(1H-benzoimidazol-2-yl-methyl)-8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-
10 triaza-spiro[4.5]decane-2,4-dione,

8-(3,5-bis-trifluoromethyl-benzoyl)-3-(2-methyl-thiazol-4-yl-methyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione,

8-(3,5-bis-trifluoromethyl-benzoyl)-3-furan-2-yl-methyl-1-phenyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione,

15 8-(3,5-bis-trifluoromethyl-benzoyl)-3-furan-2-yl-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione and

8-(3,5-bis-trifluoromethyl-benzoyl)-3-thiophen-2-yl-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione.

Preferred are further compounds, wherein X is >C=, for example the following
20 compounds:

8-(3,5-bis-trifluoromethyl-benzoyl)-2-(2-pyrrolidin-1-yl-ethyl)-4-o-tolyl-2,8-diaza-spiro[4.5]dec-3-en-1-one and

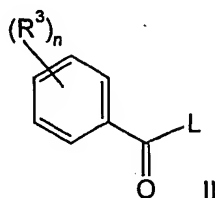
8-(3,5-bis-trifluoromethyl-benzoyl)-2-(3-dimethylamino-propyl)-4-o-tolyl-2,8-diaza-spiro[4.5]dec-3-en-1-one.

25 Further preferred are compounds, wherein X is >CH-, for example the following compound:

(rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-4-o-tolyl-2,8-diaza-spiro[4.5]decan-1-one.

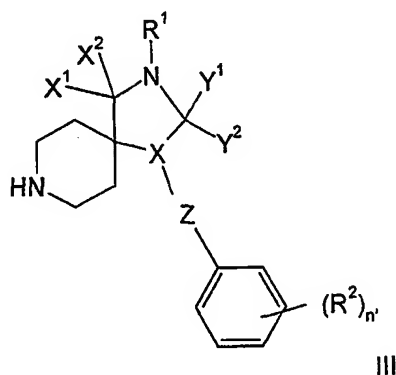
The present compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below, which process comprises

a) reacting a compound of formula

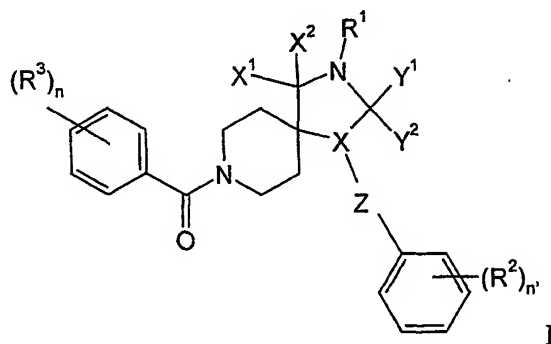


5

with a compound of formula



to a compound of formula

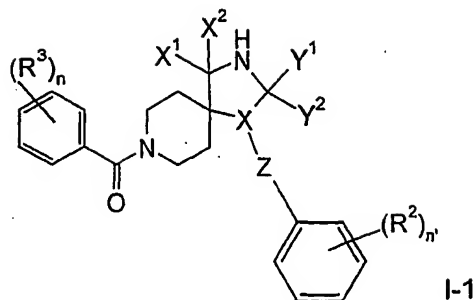


10 wherein L is a leaving group, for example halogen, such as chlorine, and the other substituents have the significances given above,

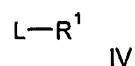
or

b) reacting a compound of formula

- 9 -

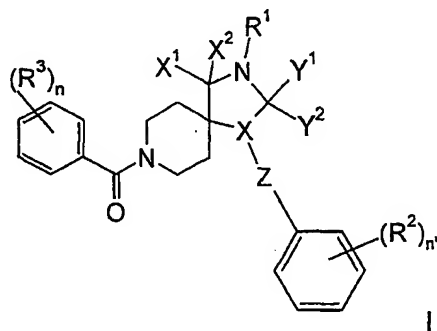


with a compound of formula



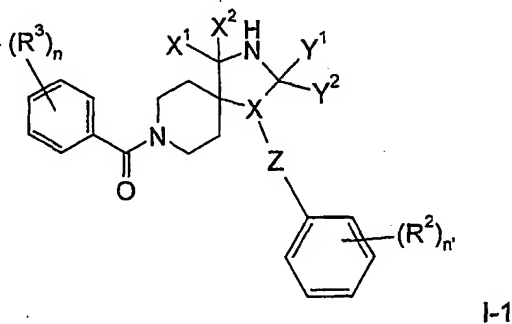
in the presence of sodium hydride or in the presence of potassium carbonate and CuCl,
 5 wherein in formula IV L is a leaving group, for example chlorine,

to give a compound of formula



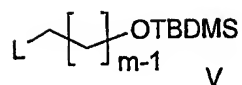
wherein the other substituents have the significances given above with the proviso
 that R¹ is not $-(CH_2)_m-OH$ and X¹/X² are not hydroxy, or

10 c) reacting a compound of formula

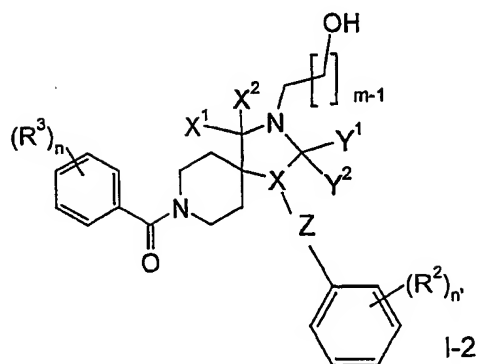


with a compound of formula

- 10 -

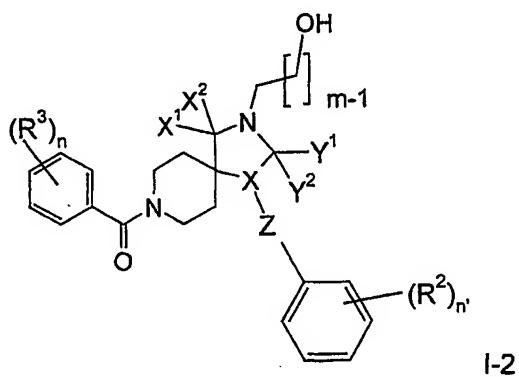


to a compound of formula



wherein TBDMS is a tert-butyl dimethylsilyl group and the further definitions of
5 substituents is given above, or

d) reacting a compound of formula

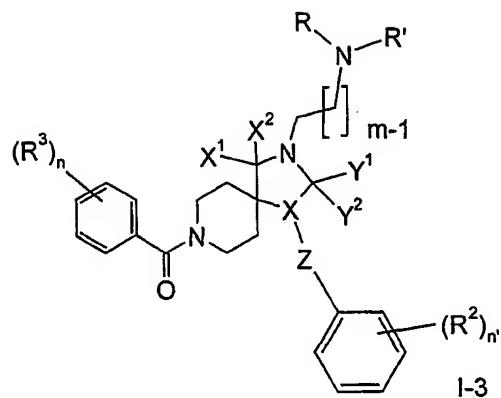


after activation as mesylate with a corresponding amine of formula



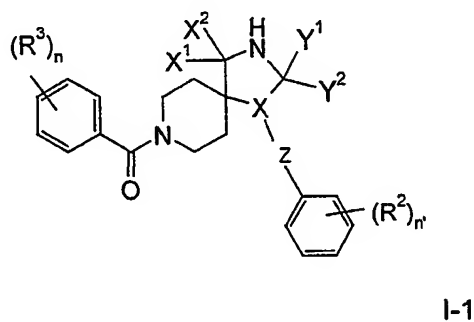
10 to give a compound of formula

- 11 -

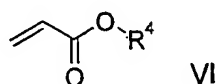


wherein the definitions of substituents are given above, or

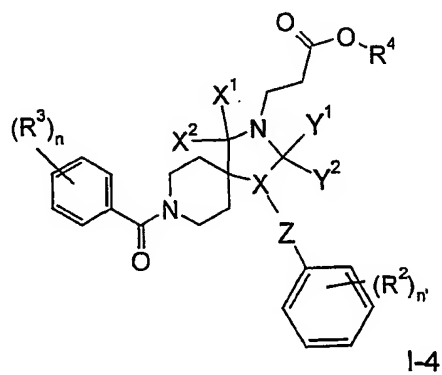
e) reacting a compound of formula



5 with a compound of formula



to a compound of formula

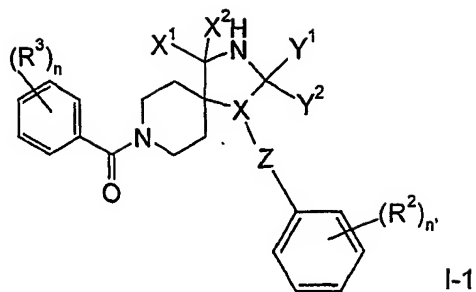


wherein R⁴ is lower alkyl and the definitions of the other substituents are given

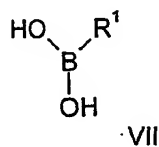
10 above, or

f) reacting a compound of formula

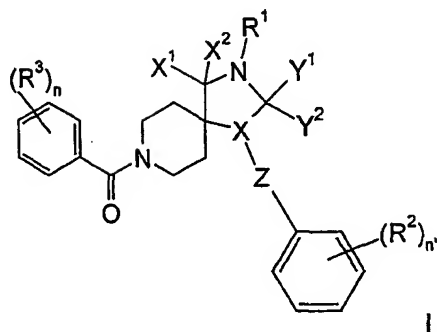
- 12 -



with a compound of formula



to a compound of formula

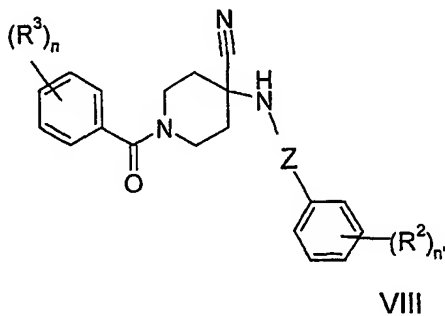


5

wherein R¹ is phenyl or heteroaryl, optionally substituted as described above and the definition of the remaining substituents is given above,

or

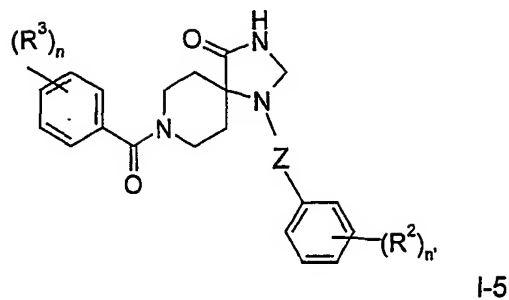
g) cyclizing a compound of formula



10

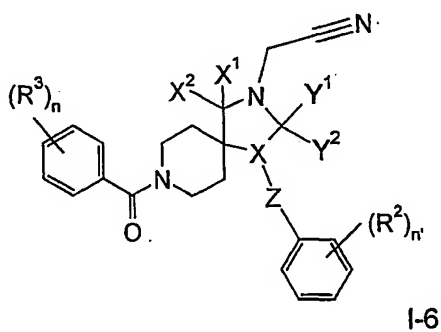
to a compound of formula

- 13 -

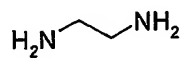


wherein the substituents are described above, or

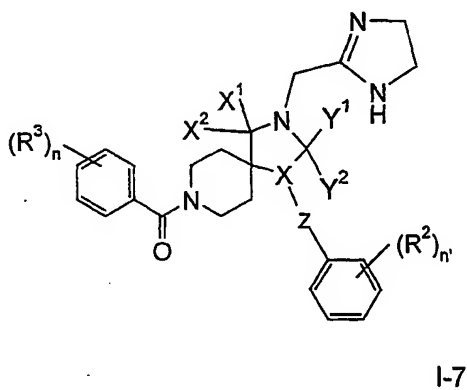
h) reacting a compound of formula



5 with



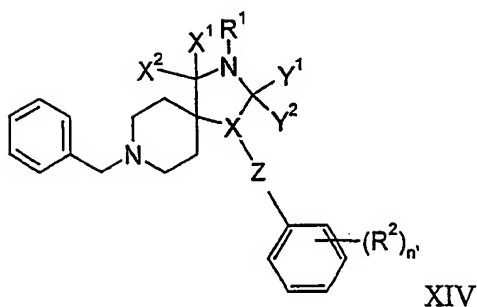
to give a compound of formula



wherein the substituents are described above, or

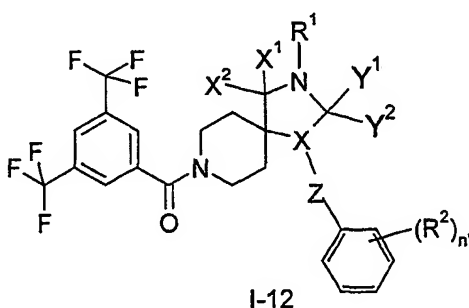
10 i) treating a compound of formula

- 14 -



with hydrogen on Pd/C and then with $(\text{CF}_3)_2\text{C}_6\text{H}_3\text{COCl}$

to obtain a compound of formula



5 wherein the substituents are given above, or

modifying one or more substituents $\text{R}^1\text{-R}^3$ within the definitions given above, and if desired, converting the compound obtained into a pharmaceutically acceptable acid addition salt.

10 The salt formation is effected at room temperature in accordance with methods which are known per se and which are familiar to any person skilled in the art. Not only salts with inorganic acids, but also salts with organic acids come into consideration. Hydrochlorides, hydrobromides, sulphates, nitrates, citrates, acetates, maleates, succinates, methan-sulphonates, p-toluenesulphonates and the like are examples of such salts.

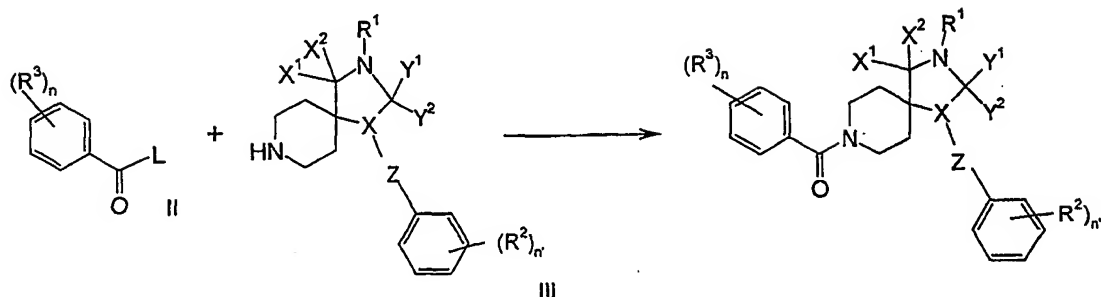
15 The following schemes 1-17 describe the processes for preparation of compounds of formula I in more detail. The starting materials are known compounds and may be prepared according to methods known in the art.

In the schemes the following abbreviations have been used:

NMP	1-methyl-2-pyrrolidinone
DME	ethylene glycol dimethyl ether
20 TBDMS	tert.-butyldimethylsilan
DMF	dimethylformamide

THF tetrahydrofuran
 TMSCN trimethylsilyl cyanide
 DIBAH diisobutylaluminium hydride

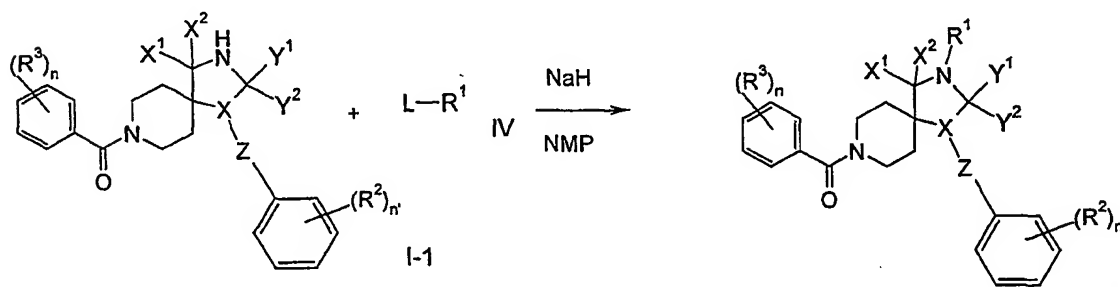
Scheme 1



wherein in scheme 1 L is a leaving group, for example halogen, such as chlorine, and the other substituents have the significances given above.

A solution of a compound of formula II, for example 3,5-bis(trifluoromethyl)benzoyl chloride in dichloromethane, is added to a mixture of a compound of formula III, which is for example 1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and triethylamine in dichloromethane. The reaction is carried out at room temperature. Compounds of examples 1 to 3 have been prepared according to scheme 1.

Scheme 2



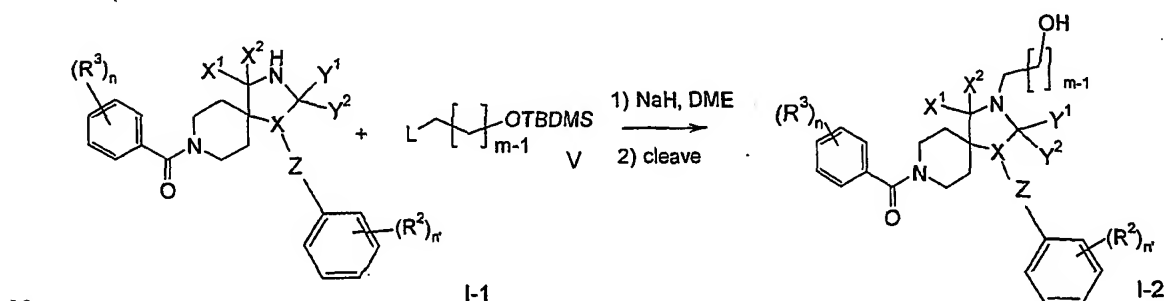
The definition of substituents is described above.

This reaction is carried out in the presence of sodium hydride and/or NMP (N-methyl-2-pyrrolidone)/1,2-dimethoxyethane. To this suspension is added a compound of formula I-1 and then a compound of formula IV is added, which is, for example, 4-(2-chlorethyl)morpholine, 3-(chloromethyl)pyridine, 2-chloro-4,6-dimethoxy-1,3,5-triazine, 1-(2-chloroethyl)piperidine, 1-(2-chloroethyl)pyrrolidine, 2-bromoacetamide, 2-chloro-N,N-dimethylacetamide, methyl bromoacetate, bromomethyl methylether, dimethyl bromomalonate, phenylglycidylether, 2,4,6-trichloropyrimidine, 2-chloro-5-(trifluoromethyl)pyridine, 3-bromo-1,1,1-trifluoro-2-propanole, 2-picolychloride, 4-

chloromethylpyridine, 2,4-dichloropyrimidine, methyl iodide, 1-benzyl-(2-chloromethyl)-imidazole, 5-chloromethyl-2-oxazolidinone, 1-chloro-2-dimethylaminoethane, 1-(2-chloroethyl)pyrrolidine, 4-chloromethyl-2-methylthiazole, 4,6-dichloropyridine, 2,3,5-trichloropyridine, 2-chloro-4-(trifluoromethyl)-pyrimidine, 2-chloro-pyridine, 2-chloro-N,N-dimethylacetamide, 3-dimethylaminopropylchloride, 4-(chloromethyl)3,5-dimethylisoxazole or 2,4-dichloro-6-methylpyrimidine.

Examples 4 to 21, 25 to 47, 70 to 82 and 86, 87 and 134 have been described in accordance with scheme 2 in more detail.

Scheme 3:

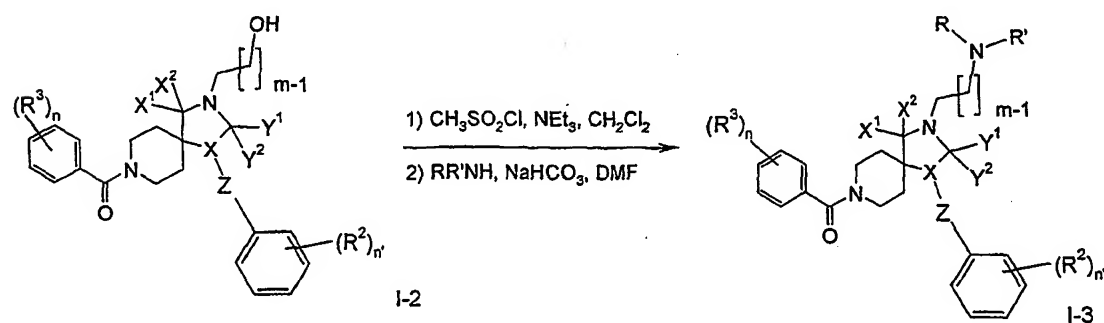


The definition of substituents is described above.

This reaction is carried out under conditions described in scheme 2, with a compound of formula I-1 and of formula V, which compound is, for example (3-bromopropoxy)-tert-butyltrimethylsilane. In a solution of HCl and ethanol the intermediate TBDMS-ether is
15 cleaved.

Examples 22 to 24 have been described in accordance with scheme 3.

Scheme 4:



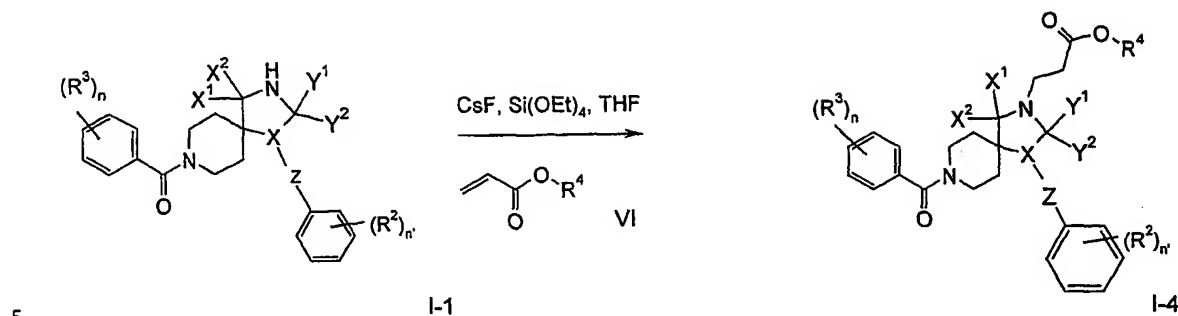
The definition of substituents is given above.

20 A solution of a compound of formula I-2 and triethylamine in dichloromethane is added to a cooled solution of methanesulfonyl chloride in dichloromethane or DMF and then sodium bicarbonate and an amine of the formula $RR'NH$ is added to obtain a compound

of formula I-3.

Examples 48 to 58 have been described in accordance with scheme 4.

Scheme 5:

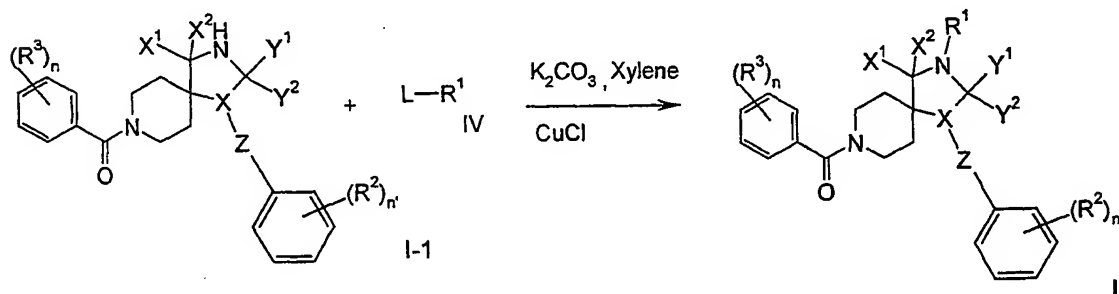


In scheme 5 R^4 is lower alkyl and the definition of the other substituents is given above.

In accordance with this scheme to a mixture of a compound of formula I-1, cesium fluoride and tetraethoxysilane, a compound of formula VI, for example ethyl acrylate, is added. The reaction is carried out at room temperature.

10 Examples 59 and 60 have been prepared as described in scheme 5.

Scheme 6

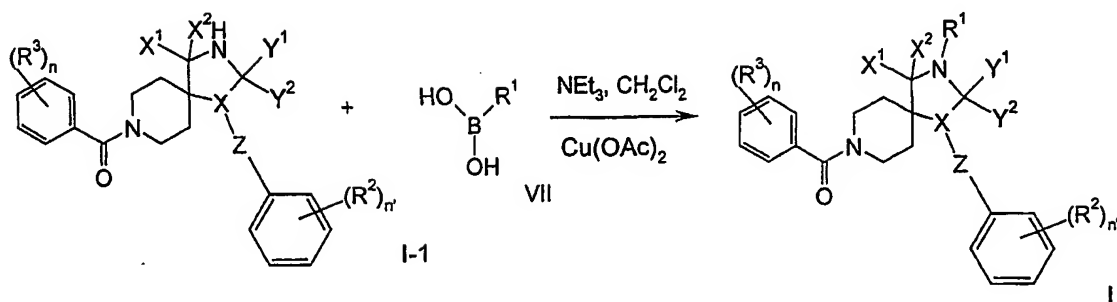


The definition of substituents is described above.

15 This reaction is carried out with a mixture of a compound of formula I-1 in the presence of potassium carbonate, CuCl and tris[2-(2-methoxyethoxy)-ethyl]-amine, and with a solution of a compound of formula IV, which is, for example, 4,6-dichloropyrimidine in xylene.

Example 61 has been described in accordance with scheme 6.

Scheme 7

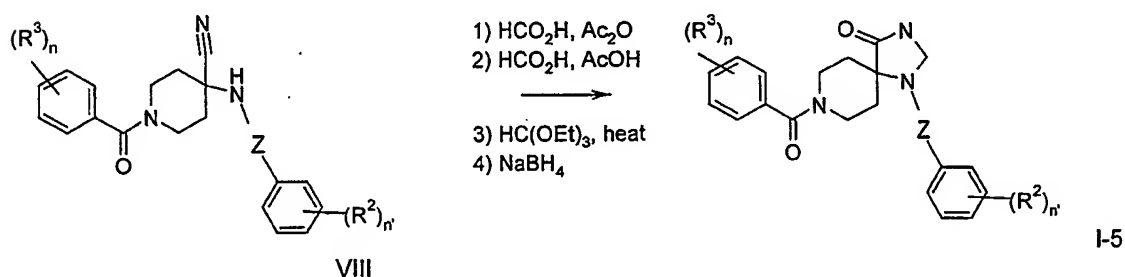


The definition of substituents is given above.

A mixture of a compound of formula I-1, a boronic acid of formula VII, cupric acetate and triethylamine in dichloromethane is stirred at room temperature. Chromatography on silica gel yielded the desired compound of formula I.

Examples 62, 83 and 84 describe the process of scheme 7 in more detail.

Scheme 8

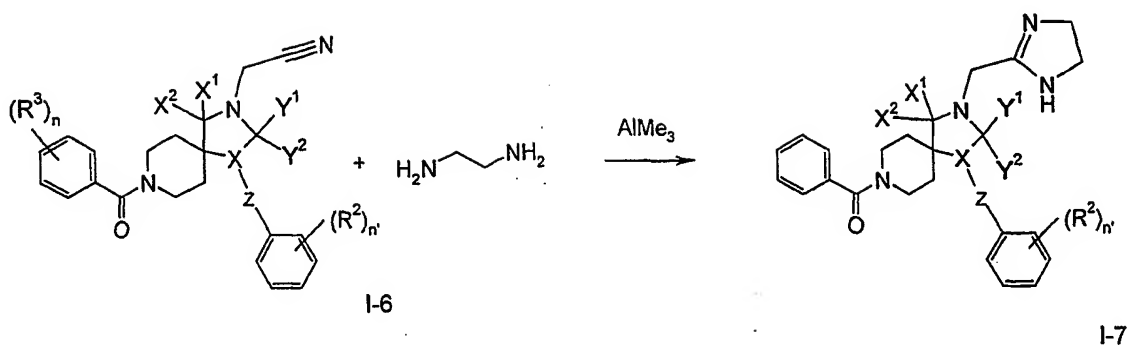


The definition of substituents is described above.

A mixture of a compound of formula VIII, formic acid and acetic anhydride is stirred at room temperature to give the intermediate N-formyl derivative, which is treated with formic acid and acetic acid to give the intermediate amide. The amide is dissolved in triethyl orthoformate and boiled. After evaporation the solid is dissolved in methanol and sodium borohydride at room temperature is added. The desired product is obtained by chromatography on silica gel.

Examples 63 to 68 and 85 describe the processes in accordance with scheme 8 in more detail.

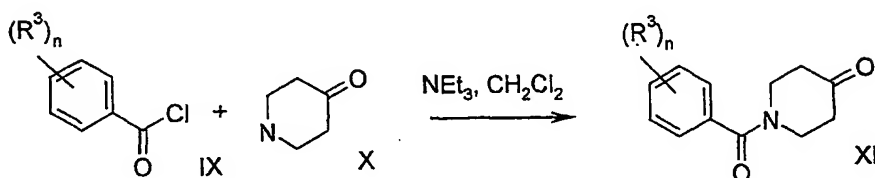
Scheme 9



The definition of substituents is described above.

- 5 An ethylenediamine-trimethylaluminium complex is added to a solution of a compound of formula I-6 in toluene. The reaction is carried out at about 120° .
Examples 69 has been described in accordance with scheme 9.

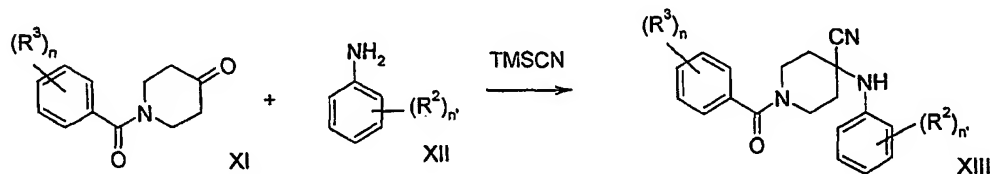
Scheme 10 (intermediates)



The definition of substituents is described above.

- 10 A solution of a compound of formula IX in dichloromethane is added with cooling to a solution of 4-piperidone trifluoroacetate and triethylamine. The reaction is carried out at room temperature.
Example A describes this process in more detail.

Scheme 11 (intermediates)

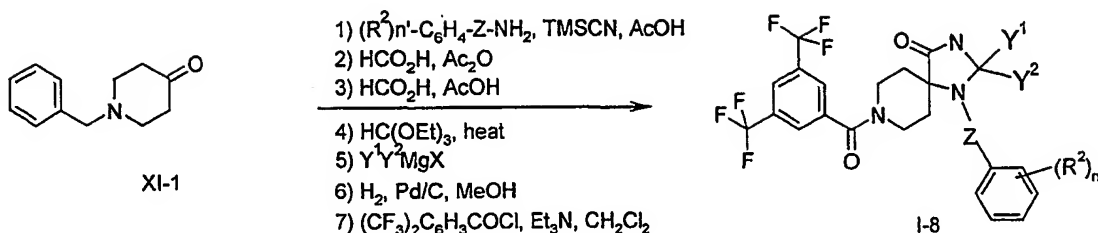


15

The definition of substituents is described above.

To a solution of a compound of formula XI in acetic acid is added with cooling a compound of formula XII, for example 3-chloroaniline, and TMSCN .
Examples B, C, D, E, F, G and H are prepared in accordance with scheme 11.

Scheme 12

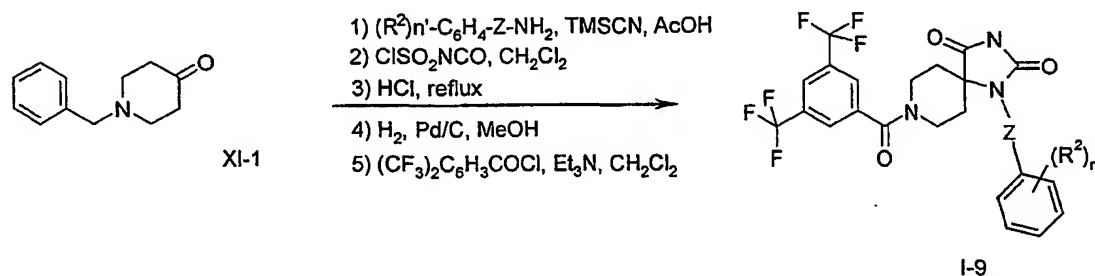


The definition of substituents is described above.

In accordance with scheme 12 to a solution of 1-benzyl-piperidin-4-one (XI-1) in acetic acid is added a compound of the formula $(R^2)_n-C_6H_4-Z-NH_2$, for example aniline, and TMSCN. To a solution of the intermediate amino nitrile in formic acid is added with cooling acetic anhydride and the obtained foam is dissolved in formic acid and acetic acid. The intermediate is cyclized by boiling in triethylorthoformate and subsequently treated with a Grignard reagent, for example with methylmagnesium bromide. The intermediate is treated with hydrogen and palladium on charcoal in methanol. The last step is the treatment of the obtained solution with 3,5-bis-trifluoromethyl benzoylchloride to obtain a compound of formula I-8.

Examples 91 to 109, 112, 114 to 120 and 132 describe the processes in accordance with scheme 12 in more detail.

Scheme 13

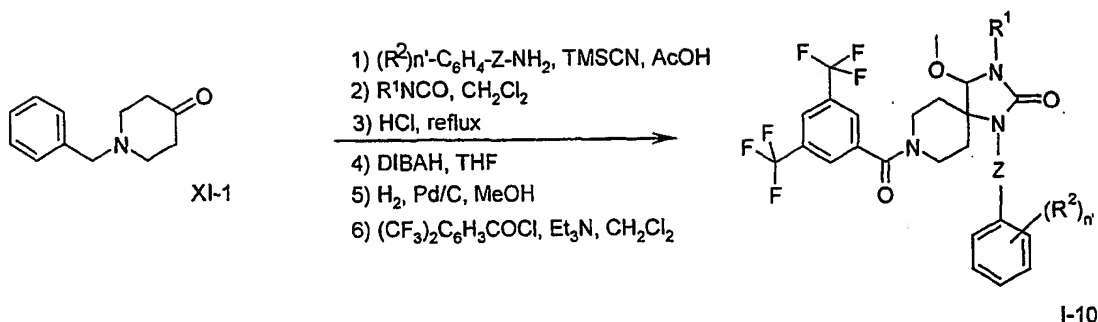


The definition of substituents is described above.

To a solution of the compound of formula XI-1 in acetic acid a compound of formula $(R^2)_n-C_6H_4-Z-NH_2$, for example aniline, and TMSCN are added. Then, to a solution of the intermediate amino nitrile, chlorosulfonyl isocyanate is added. The solid is suspended in hydrochloric acid and refluxed. The intermediate is treated with hydrogen and palladium on charcoal. The last step is the treatment with $(CF_3)_2C_6H_3COCl$ to give a compound of formula I-9.

Examples 110, 111 and 113 are described in more detail in accordance with scheme 13.

Scheme 14

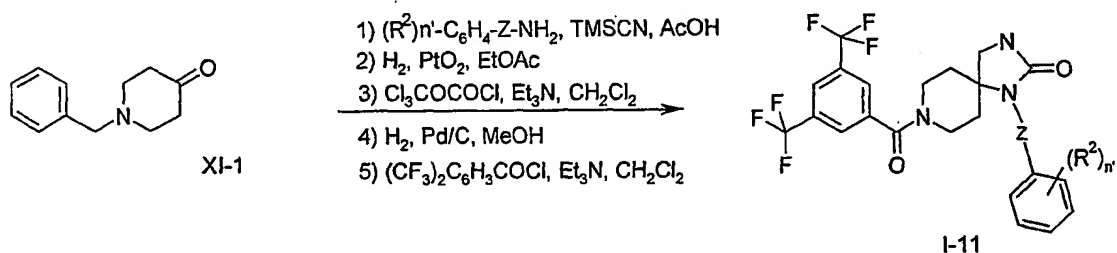


The definition of substituents is described above.

To a solution of 1-benzyl-piperidin-4-one (XI-1) in acetic acid is added a compound of formula $(R^2)_n-C_6H_4-Z-NH_2$, for example aniline, and TMSCN. To a solution of the obtained intermediate amino nitrile in dichloromethane is added chlorosulfonyl isocyanate. The obtained white solid is suspended in HCl and refluxed. The reduction is then performed with diisobutyl aluminium hydride. The intermediate n-benzyl protected spiro piperidine is treated with hydrogen and palladium on charcoal. After stirring in a hydrogen atmosphere at room temperature $(CF_3)_2C_6H_3COCl$ is added to give a compound of formula I-10.

Examples 129 and 130 are described in accordance with scheme 14.

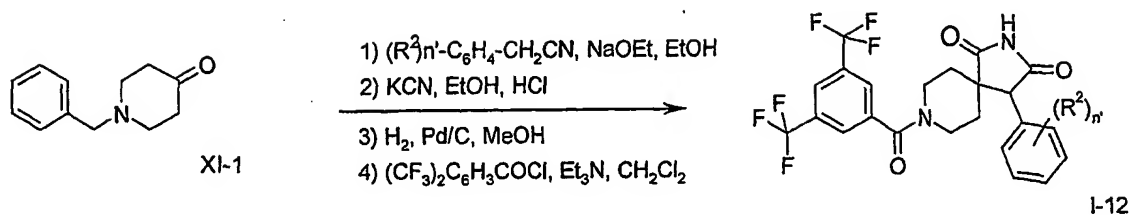
Scheme 15



15 The definition of substituents is described above.

To a solution of 1-benzyl-piperidin-4-one (XI-1) in acetic acid is added a compound of formula $(R^2)_n-C_6H_4-Z-NH_2$, for example o-toluidine, and TMSCN. The solution of the obtained intermediate amino nitrile is dissolved in acetic acid PtO_2 , and the reaction mixture is hydrogenated at room temperature. To the solution of the obtained intermediate in dichloromethane and triethylamine is added trichloromethyl chloroformate at about $-20^\circ C$. The obtained intermediate N-benzyl protected spiropiperidine is treated with hydrogen and palladium on charcoal. After stirring in a hydrogen atmosphere at room temperature $(CF_3)_2C_6H_3COCl$ is added to give a compound of formula I-11. Example 131 is prepared in accordance with scheme 15.

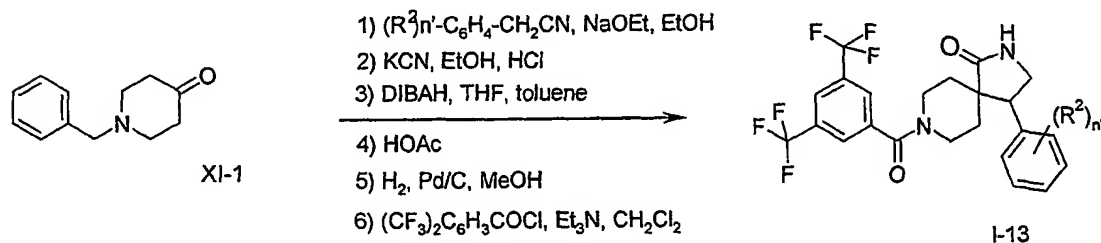
Scheme 16



The definition of substituents is described above.

- 5 To a solution sodium ethoxide is added benzyl cyanide and N-benzyl-4-piperidone (XI-1) and the reaction is run at 85 °C for 3 h. Workup with concentrated hydrochloric gives the intermediate (1-benzyl-piperidin-4-ylidene)-phenyl-acetonitrile which is treated with potassium cyanide. The obtained intermediate N-benzyl protected spiropiperidine is treated with hydrogen and palladium on charcoal. After stirring in a hydrogen atmosphere
- 10 at room temperature $(\text{CF}_3)_2\text{C}_6\text{H}_3\text{COCl}$ is added to give a compound of formula I-12. Example 156 is prepared in accordance with scheme 16.

Scheme 17



The definition of substituents is described above.

- 15 To a solution sodium ethoxide is added benzyl cyanide and N-benzyl-4-piperidone (XI-1) and the reaction is run at 85 °C for 3 h. Workup with concentrated hydrochloric gives the intermediate (1-benzyl-piperidin-4-yl-idene)-phenyl-acetonitrile which is treated with potassium cyanide. Reduction of one carbonyl group is performed with an excess of diisobutylaluminium hydride and elimination is performed with acetic acid. The obtained
- 20 intermediate N-benzyl protected spiropiperidine is treated with hydrogen and palladium on charcoal. After stirring in a hydrogen atmosphere at room temperature $(\text{CF}_3)_2\text{C}_6\text{H}_3\text{COCl}$ is added to give a compound of formula I-13. Example 161 is prepared in accordance with scheme 17.

As mentioned earlier, the compounds of formula I and their pharmaceutically usable addition salts possess valuable pharmacological properties. It has been found that the compounds of the present invention are antagonists of the Neurokinin 1 (NK-1, substance P) receptor.

5 The compounds were investigated in accordance with the tests given hereinafter.

The affinity of test compounds for the NK₁ receptor was evaluated at human NK₁ receptors in CHO cells infected with the human NK₁ receptor (using the Semliki virus expression system) and radiolabelled with [³H]substance P (final concentration 0.6 nM). Binding assays were performed in HEPES buffer (50 mM, pH 7.4) containing BSA (0.04 %) leupeptin (8 µg / ml), MnCl₂ (3mM) and phosphoramidon (2 µM). Binding assays
10 consisted of 250 µl of membrane suspension (1.25x10⁵ cells / assay tube), 0.125 µl of buffer of displacing agent and 125 µl of [³H]substance P. Displacement curves were determined with at least seven concentrations of the compound. The assay tubes were incubated for 60 min at room temperature after which time the tube contents were rapidly filtered under
15 vacuum through GF/C filters presoaked for 60 min with PEI (0.3%) with 2 x 2 ml washes of HEPES buffer (50 mM, pH 7.4). The radioactivity retained on the filters was measured by scintillation counting. All assays were performed in triplicate in at least 2 separate experiments.

The affinity to the NK-1 receptor, given as pKi, is in the range of 6.5-8.8 for the
20 exemplified compounds. Examples of such compounds are

Example No.	pKi
6	8.66
26	7.47
39	7.03
45	8.29
58	8.08
70	8.37
91	8.12
137	8.34

170	7.96
176	8.12

The compounds of formula I as well as their pharmaceutically usable acid addition salts can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula I and their pharmaceutically usable acid addition salts can be processed with pharmaceutically inert, inorganic or organic excipients for the production of tablets, coated tablets, dragees and hard gelatine capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc can be used as such excipients e.g. for tablets, dragées and hard gelatine capsules.

Suitable excipients for soft gelatine capsules are e.g. vegetable oils, waxes, fats, semi-solid and liquid polyols etc.

Suitable excipients for the manufacture of solutions and syrups are e.g. water, polyols, saccharose, invert sugar, glucose etc.

Suitable excipients for injection solutions are e.g. water, alcohols, polyols, glycerol, vegetable oils etc.

Suitable excipients for suppositories are e.g. natural or hardened oils, waxes, fats, semi-liquid or liquid polyols etc.

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 10 to 1000 mg per person of a compound of general formula I should be appropriate, although the above upper limit can also be exceeded when necessary.

The following Examples illustrate the present invention without limiting it. All temperatures are given in degrees Celsius.

Example 1

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

- 5 A solution of 3,5-bis(trifluoromethyl)benzoyl chloride (2.3 mL, 13 mmol) in dichloromethane (50 mL) was added with stirring to a mixture of 1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one (2.9 g, 13mmol) and triethylamine (3.5 mL, 25 mmol) in dichloromethane (250 mL) at room temperature. Stirring was continued for 2 h. Water (150 mL) was added, the phases were separated and the water phase was extracted twice
10 with dichloromethane (100 mL). Organic phases were pooled, washed with brine (200 mL), dried with Na₂SO₄ and the solvent was evaporated. Chromatography on silica gel (ethylacetate/n-hexane 1:1) yielded the desired product (5.3 g, 89 %) m.p. 251 °C and MS: m/e = 472.1 (M+H⁺).

Example 2

15 1-Phenyl-8-(3,4,5-trimethoxy-benzoyl)-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: m/e = 426.4 (M+H⁺), was prepared in accordance with the general method of example 1 from 3,4,5-trimethoxybenzoyl chloride and 1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one.

Example 3

20 8-(3-Fluoro-5-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: m/e = 422.3 (M+H⁺), was prepared in accordance with the general method of example 1 from 3-fluoro-5-(trifluoromethyl)benzoyl chloride and 1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one.

Example 4

25 8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(2-morpholin-4-yl-ethyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

- Sodium hydride (34 mg, 60 %) was suspended in N-methyl-2-pyrrolidone (2 mL) and 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one (200 mg) was added with stirring. After 5 minutes stirring at room temperature 4-(2-
30 chlorethyl)morpholine hydrochloride (79 mg) was added. The mixture was heated to 100

°C with stirring and kept for 1 h at that temperature. After cooling, saturated sodium bicarbonate solution was added and the mixture was extracted with ethylacetate. Organic phases were pooled, dried with Na₂SO₄ and the solvent was evaporated. Chromatography on silica gel (ethylacetate) yielded the desired product (180 mg, 73%), MS: m/e = 585.1 (M+H⁺).

Example 5

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-phenyl-3-pyridin-3-yl-methyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: m/e = 563.3 (M+H⁺), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and 3-(chloromethyl)pyridine hydrochloride in 1,2-dimethoxyethane as solvent.

Example 6

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(4,6-dimethoxy-[1,3,5]triazin-2-yl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: m/e = 611.0 (M+H⁺), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and 2-chloro-4,6-dimethoxy-1,3,5-triazine in 1,2-dimethoxyethane as solvent.

Example 7

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-phenyl-3-(2-piperidin-1-yl-ethyl)-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: m/e = 583.2 (M+H⁺), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and 1-(2-chloroethyl)piperidine hydrochloride.

Example 8

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-phenyl-3-(2-pyrrolidin-1-yl-ethyl)-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: m/e = 569.2 (M+H⁺), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and 1-(2-chloroethyl)pyrrolidine hydrochloride.

Example 9

2-[8-(3,5-Bis-trifluoromethyl-benzoyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetamide

The title compound, MS: $m/e = 529.2$ ($M+H^+$), was prepared in accordance with the
5 general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and 2-bromoacetamide in 1,2-dimethoxyethane as solvent.

Example 10

2-[8-(3,5-Bis-trifluoromethyl-benzoyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-N,N-dimethyl-acetamide

10 The title compound, MS: $m/e = 557.2$ ($M+H^+$), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and 2-chlor-N,N-dimethyacetamide in 1,2-dimethoxyethane as solvent.

Example 11

15 [8-(3,5-Bis-trifluoromethyl-benzoyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid methyl ester

The title compound, MS: $m/e = 544.2$ ($M+H^+$), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and methyl bromoacetate in 1,2-dimethoxyethane as solvent.

20

Example 12

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-methoxymethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 516.2$ ($M+H^+$), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and bromomethyl methylether in 1,2-dimethoxyethane as
25 solvent.

Example 13

2-[8-(3,5-Bis-trifluoromethyl-benzoyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-malonic acid dimethyl ester

The title compound, MS: $m/e = 602.0$ ($M+H^+$), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and dimethyl bromomalonate in 1,2-dimethoxyethane as solvent.

5

Example 14

(R,S)-8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(2-hydroxy-3-phenoxy-propyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 622.1$ ($M+H^+$), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and phenylglycidylether in 1,2-dimethoxyethane as solvent.

10

Example 15

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(4,6-dichloro-pyrimidin-2-yl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 618.0$ ($M+H^+$), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and 2,4,6-trichloropyrimidine in 1,2-dimethoxyethane as solvent.

15

Example 16

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-phenyl-3-(5-trifluoromethyl-pyridin-2-yl)-1,3,8-triaza-spiro[4.5]decan-4-one

20

The title compound, MS: $m/e = 617.1$ ($M+H^+$), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and 2-chloro-5-(trifluoromethyl)pyridine in 1,2-dimethoxyethane as solvent.

25

Example 17

(R,S)-8-(3,5-Bis-trifluoromethyl-benzoyl)-1-phenyl-3-(3,3,3-trifluoro-2-hydroxy-propyl)-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 584.0$ ($M+H^+$), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and 3-bromo-1,1,1-trifluoro-2-propanol.

30

Example 18

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-phenyl-3-pyridin-2-yl-methyl-1,3,8-triaza-spiro[4.5]decan-4-one

5 The title compound, MS: $m/e = 563.3$ ($M+H^+$), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and 2-picolylchloride hydrochloride in 1,2-dimethoxyethane as solvent.

Example 19

10 8-(3,5-Bis-trifluoromethyl-benzoyl)-1-phenyl-3-pyridin-4-yl-methyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 563.3$ ($M+H^+$), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and 4-chloromethylpyridine hydrochloride in 1,2-dimethoxyethane as solvent.

15 Example 20

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(4-chloro-pyrimidin-2-yl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

20 The title compound, MS: $m/e = 584.1$ ($M+H^+$), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and 2,4-dichloropyrimidine in 1,2-dimethoxyethane as solvent.

Example 21

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(4-chloro-6-methyl-pyrimidin-2-yl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

25 The title compound, MS: $m/e = 598.0$ ($M+H^+$), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and 2,4-dichloro-6-methylpyrimidine in 1,2-dimethoxyethane as solvent.

Example 22

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(3-hydroxy-propyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 530.2$ ($M+H^+$), was prepared in accordance with the
5 general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and (3-bromopropoxy)-tert.-butyldimethylsilane in 1,2-dimethoxyethane as solvent. HCl in ethanol (3% conc.) cleaved the intermediate TBDMS-ether.

Example 23

10 8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(2-hydroxy-ethyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 530.2$ ($M+H^+$), was prepared in accordance with the
general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one and (3-bromoethoxy)-tert.-butyldimethylsilane. HCl in
15 ethanol (3% conc.) cleaved the intermediate TBDMS-ether.

Example 24

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(2-hydroxy-ethyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 516.2$ ($M+H^+$), was prepared in accordance with the
20 general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and 2-chloroethoxytrimethylsilane in 1,2-dimethoxyethane as solvent. Silicagel chromatography cleaved the intermediate TMS-ether.

Example 25

25 8-(3,5-Bis-trifluoromethyl-benzoyl)-1-phenyl-3-pyrimidin-2-yl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 550.1$ ($M+H^+$), was prepared in accordance with the
general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and 2-chloropyrimidine.

Example 26

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(3,5-dichloro-pyridin-2-yl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

5 The title compound, MS: $m/e = 617.0$ ($M+H^+$), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and 2,3,5-trichloropyridine in 1,2-dimethoxyethane as solvent.

Example 27

10 2-[8-(3,5-Bis-trifluoromethyl-benzoyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-6-methyl-nicotinonitrile

The title compound, MS: $m/e = 588.2$ ($M+H^+$), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and 2-chloro-3-cyanopyridine in 1,2-dimethoxyethane as solvent.

15 Example 28

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(3-chloro-5-trifluoromethyl-pyridin-2-yl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

20 The title compound, MS: $m/e = 651.0$ ($M+H^+$), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and 2,3-dichloro-5-(trifluoromethyl)pyridine in 1,2-dimethoxyethane as solvent.

Example 29

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(5-ethyl-pyrimidin-2-yl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

25 The title compound, MS: $m/e = 578.0$ ($M+H^+$), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and 2-chloro-5-ethylpyrimidine in 1,2-dimethoxyethane as solvent.

Example 30

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-phenyl-3-(4-trifluoromethyl-pyrimidin-2-yl)-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 618.1$ ($M+H^+$), was prepared in accordance with the
5 general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and 2-chloro-4-(trifluoromethyl)pyrimidine in 1,2-dimethoxyethane as solvent.

Example 31

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(3-chloro-pyrazin-2-yl)-1-phenyl-1,3,8-triaza-
10 spiro[4.5]decan-4-one

The title compound, MS: $m/e = 584.1$ ($M+H^+$), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and 2,3-dichloropyrazine in 1,2-dimethoxyethane as solvent.

Example 32

15 [8-(3,5-Bis-trifluoromethyl-benzoyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetic acid ethyl ester

The title compound, MS: $m/e = 558.2$ ($M+H^+$), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and ethyl bromoacetate in 1,2-dimethoxyethane as solvent.

20

Example 33

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(3-chloro-quinoxalin-2-yl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 634.0$ ($M+H^+$), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-
25 triaza-spiro[4.5]decan-4-one and 2,3-dichloroquinoxaline in 1,2-dimethoxyethane as solvent.

Example 34

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(6-chloro-pyrazin-2-yl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 584.1$ ($M+H^+$), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and 2,6-dichloropyrazine in 1,2-dimethoxyethane as solvent.

Example 35

- 5 8-(3,5-Bis-trifluoromethyl-benzoyl)-1-phenyl-3-pyrazin-2-yl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 550.1$ ($M+H^+$), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and 2-chloropyrazine in 1,2-dimethoxyethane as solvent.

10

Example 36

[8-(3,5-Bis-trifluoromethyl-benzoyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetonitrile

- 15 The title compound, MS: $m/e = 510.1$ (M^+), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and bromoacetonitrile in 1,2-dimethoxyethane as solvent.

Example 37

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(4,6-dimethoxy-pyrimidin-2-yl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

- 20 The title compound, MS: $m/e = 610.0$ ($M+H^+$), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and 2-chloro-4,6-dimethoxypyrimidine.

Example 38

(S)-8-(3,5-Bis-trifluoromethyl-benzoyl)-1-phenyl-3-(4,4,4-trifluoro-3-hydroxy-butyl)-1,3,8-triaza-spiro[4.5]decan-4-one

- 25 The title compound, MS: $m/e = 598.0$ ($M+H^+$), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and toluene-4-sulfonic acid (S)-4,4,4-trifluoro-3-hydroxy-butyl ester in 1,2-dimethoxyethane as solvent.

Example 39

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(3,4-dichloro-phenyl)-3-(4,6-dimethoxy-[1,3,5]triazin-2-yl)-1,3,8-triaza-spiro[4.5]decan-4-one

5 The title compound, MS: $m/e = 679.0$ ($M+H^+$), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-(3,4-dichloro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one and 2-chloro-4,6-dimethoxy-1,3,5-triazine in 1,2-dimethoxyethane as solvent.

Example 40

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(3-chloro-phenyl)-3-(4,6-dimethoxy-[1,3,5]triazin-2-yl)-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 645.1$ ($M+H^+$), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-(3-chloro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one and 2-chloro-4,6-dimethoxy-1,3,5-triazine in 1,2-dimethoxyethane as solvent.

15

Example 41

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(4,6-dimethoxy-[1,3,5]triazin-2-yl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 625.1$ ($M+H^+$), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one and 2-chloro-4,6-dimethoxy-1,3,5-triazine in 1,2-dimethoxyethane as solvent.

20

Example 42

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-3-(4,6-dimethoxy-[1,3,5]triazin-2-yl)-1,3,8-triaza-spiro[4.5]decan-4-one

25 The title compound, MS: $m/e = 645.0$ ($M+H^+$), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one and 2-chloro-4,6-dimethoxy-1,3,5-triazine in 1,2-dimethoxyethane as solvent.

Example 43

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(4-chloro-phenyl)-3-(4,6-dimethoxy-[1,3,5]triazin-2-yl)-1,3,8-triaza-spiro[4.5]decan-4-one

5 The title compound, MS: $m/e = 645.1 (M+H^+)$, was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-(4-chloro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one and 2-chloro-4,6-dimethoxy-1,3,5-triazine in 1,2-dimethoxyethane as solvent.

Example 44

10 8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-3-pyridin-3-yl-methyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 597.0 (M+H^+)$, was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one and 3-(chloromethyl)pyridine hydrochloride in 1,2-dimethoxyethane as solvent.

15

Example 45

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-pyridin-3-yl-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one

20 The title compound, MS: $m/e = 577.0 (M+H^+)$, was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one and 3-(chloromethyl)pyridine hydrochloride in 1,2-dimethoxyethane as solvent.

Example 46

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(2-methoxy-phenyl)-3-pyridin-3-yl-methyl-1,3,8-triaza-spiro[4.5]decan-4-one

25 The title compound, MS: $m/e = 592.1 (M^+)$, was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-(2-methoxy-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one and 3-(chloromethyl)pyridine hydrochloride in 1,2-dimethoxyethane as solvent.

Example 47

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(4,6-dimethoxy-[1,3,5]triazin-2-yl)-1-(2-methoxy-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 640.2 (M^+)$, was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-(2-methoxy-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one and 2-chloro-4,6-dimethoxy-1,3,5-triazine in 1,2-dimethoxyethane as solvent.

Example 48

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(3-imidazol-1-yl-propyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

A solution of 8-(3,5-bis-trifluoromethyl-benzoyl)-3-(3-hydroxy-propyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one (128 mg, 0.25 mmol) and triethylamine (35 μ L, 0.27 mmol) in dichloromethane (2 mL) was cooled to 0 °C. A solution of methanesulfonyl chloride (19 μ L, 0.25 mmol) in dichloromethane (0.5 mL) was added and the mixture was stirred for 4h at 0 °C. Sodium bicarbonate (saturated solution, 2.5 mL) was added, the phases were separated, the organic phase was dried with Na_2SO_4 and the solvent was evaporated. Chromatography on silica gel (ethylacetate/n-hexane 1:1) yielded the intermediate mesylate. The mesylate was dissolved in dimethylformamide (6 mL), sodium bicarbonate (70 mg, 0.74 mmol) and imidazole (26 mg, 0.37 mmol) was added and the mixture stirred for 2 d at 80 °C. Filtration and evaporation of the solvent yielded a residue which was purified by chromatography on silica gel (CH_2Cl_2 /MeOH 9:1) to yield the desired product (23 mg, 16 %), MS: $m/e = 580.1 (M+H^+)$.

Example 49

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(3-isopropylamino-propyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 571.1 (M+H^+)$, was prepared in accordance with the general method of example 48 from 8-(3,5-bis-trifluoromethyl-benzoyl)-3-(3-hydroxy-propyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and isopropylamine.

Example 50

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-[3-(4-methyl-piperazin-1-yl)-propyl]-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 612.2$ ($M+H^+$), was prepared in accordance with the general method of example 48 from 8-(3,5-bis-trifluoromethyl-benzoyl)-3-(3-hydroxy-propyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and 1-methylpiperazine.

Example 51

- 5 8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(3-dimethylamino-propyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 557.2$ ($M+H^+$), was prepared in accordance with the general method of example 48 from 8-(3,5-bis-trifluoromethyl-benzoyl)-3-(3-hydroxy-propyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and dimethylamine.

- 10 Example 52

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(2-imidazol-1-yl-ethyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

- The title compound, MS: $m/e = 566.2$ ($M+H^+$), was prepared in accordance with the general method of example 49 from 8-(3,5-bis-trifluoromethyl-benzoyl)-3-(2-hydroxy-ethyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and imidazole.

Example 53

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(2-isopropylamino-ethyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

- The title compound, MS: $m/e = 557.2$ ($M+H^+$), was prepared in accordance with the general method of example 48 from 8-(3,5-bis-trifluoromethyl-benzoyl)-3-(2-hydroxy-ethyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and isopropylamine.

Example 54

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-[2-(4-methyl-piperazin-1-yl)-ethyl]-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

- 25 The title compound, MS: $m/e = 598.1$ ($M+H^+$), was prepared in accordance with the general method of example 48 from 8-(3,5-bis-trifluoromethyl-benzoyl)-3-(2-hydroxy-ethyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and 1-methylpiperazine.

Example 55

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(2-dimethylamino-ethyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 543.2$ ($M+H^+$), was prepared in accordance with the
5 general method of example 48 from 8-(3,5-bis-trifluoromethyl-benzoyl)-3-(2-hydroxy-ethyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and dimethylamine.

Example 56

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(2-dimethylamino-ethyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one

10 The title compound, MS: $m/e = 557.2$ ($M+H^+$), was prepared in accordance with the general method of example 48 from 8-(3,5-bis-trifluoromethyl-benzoyl)-3-(2-hydroxy-ethyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one and dimethylamine.

Example 57

15 8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(2-isopropylamino-ethyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 571.1$ ($M+H^+$), was prepared in accordance with the general method of example 48 from 8-(3,5-bis-trifluoromethyl-benzoyl)-3-(2-hydroxy-ethyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one and isopropylamine.

Example 58

20 8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(2-pyrrolidin-1-yl-ethyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 583.2$ ($M+H^+$), was prepared in accordance with the general method of example 48 from 8-(3,5-bis-trifluoromethyl-benzoyl)-3-(2-hydroxy-ethyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one and pyrrolidine.

25

Example 59

3-[8-(3,5-Bis-trifluoromethyl-benzoyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-propionic acid ethyl ester

To a mixture of 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one (1.0 g, 2.1 mmol), cesium fluoride (32 mg, 0.21 mmol) and

tetraethoxysilane (475 μ L, 2.1 mmol) in THF (10 mL) was added ethyl acrylate (254 μ L, 2.3 mmol). The mixture was stirred for 1 d at room temperature. Evaporation of the solvent yielded a residue which was purified by chromatography on silica gel (ethyl acetate/n-hexane 1:2) to yield the desired product (0.9 g, 75 %), MS: $m/e = 572.1$ ($M+H^+$).

5

Example 60

3-[8-(3,5-Bis-trifluoromethyl-benzoyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-propionic acid methyl ester

The title compound, MS: $m/e = 558.2$ ($M+H^+$), was prepared in accordance with the general method of example 59 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and methyl acrylate.

10

Example 61

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(6-chloro-pyrimidin-4-yl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

A mixture of 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.1 g, 0.21 mmol), potassium carbonate (59 mg, 0.42 mmol), CuCl (2 mg, 0.021 mmol), tris[2-(2-methoxyethoxy)-ethyl]-amine (1.5 μ L) and 4,6-dichloropyrimidine (32 mg, 0.21 mmol) in xylene (5 mL) was stirred and boiled for 18 h. The mixture was cooled, washed with water, ammonia in water (10 %) and water again. Evaporation of the solvent yielded a residue which was purified by chromatography on silica gel (ethyl acetate/n-hexane 1:2) to yield the desired product (29 mg, 24 %), m.p. 212-214 °C and MS: $m/e = 584.1$ ($M+H^+$).

20

Example 62

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-phenyl-3-pyridin-4-yl-1,3,8-triaza-spiro[4.5]decan-4-one

A mixture of 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.1 g, 0.21 mmol), 4-pyridylboronic acid (52 mg, 0.42 mmol), cupric acetate (58 mg, 0.32 mmol) and triethylamine (60 μ L, 0.42 mmol) in dichloromethane (2 mL) was stirred for 2 d at room temperature. Chromatography on silica gel (ethyl acetate) yielded the desired product (26 mg, 21 %), MS: $m/e = 549.1$ ($M+H^+$).

25

Example 63

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(3-chloro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one

To a solution of 1-(3,5-bis-trifluoromethyl-benzoyl)-4-(3-chloro-phenylamino)-
5 piperidine-4-carbonitrile (6.2 g, 13 mmol) in formic acid (80 mL) was added with cooling acetic anhydride (80 mL). Stirring continued for 2 h at room temperature. Evaporation of the solvent yielded 7.2 g white foam, which was used without further purification in the next step.

The solid was dissolved in formic acid (74 mL) and acetic acid was added (7.4 mL). The
10 solution was stirred at room temperature over night. The solvents were evaporated, saturated sodium bicarbonate solution (150 mL) was added and the mixture was extracted with ethylacetate. The organic phases were pooled, dried with Na₂SO₄ and the solvent was evaporated. The residue was a white foam (7.5 g), which was used without further purification in the next step.

15 The solid was dissolved in triethyl orthoformate (320 mL) and boiled for a week. After cooling the solvent was evaporated to yield 8.5 g brownish foam which was used without further purification in the next step.

The solid was dissolved in methanol (300 mL), sodium borohydride (1.03 g, 27 mmol) was added to the solution and the mixture was stirred for 1 h at room temperature and for 1 h
20 at 60 °C. After cooling the solvent was evaporated, the residue was dissolved in dichloromethane (250 mL) and washed with ice cold ammonia (12%). The phases were separated, the water phase was extracted with dichloromethane, and organic phases were pooled and dried with MgSO₄. Evaporation yielded 8.1 g light brown residue. Chromatography on silica gel (dichloromethane/methanol 50:1) yielded the desired
25 product (2.7 g, 41 %), m.p. 235-236 °C and MS: m/e = 506.2 (M+H⁺).

Example 64

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(4-chloro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, m.p. 233-235 °C and MS: m/e = 506.2 (M+H⁺), was prepared in
30 accordance with the general method of example 63 from 1-(3,5-bis-trifluoromethyl-benzoyl)-4-(4-chloro-phenylamino)-piperidine-4-carbonitrile.

Example 65

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(3,4-dichloro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, m.p. 220-222 °C and MS: $m/e = 540.1$ ($M+H^+$), was prepared in accordance with the general method of example 63 from 1-(3,5-bis-trifluoromethyl-benzoyl)-4-(3,4-dichloro-phenylamino)-piperidine-4-carbonitrile.

Example 66

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, m.p. 164-168 °C and MS: $m/e = 486.3$ ($M+H^+$), was prepared in accordance with the general method of example 63 from 1-(3,5-bis-trifluoromethyl-benzoyl)-4-o-tolylamino-piperidine-4-carbonitrile.

Example 67

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, m.p. 157-159 °C and MS: $m/e = 506.2$ ($M+H^+$), was prepared in accordance with the general method of example 63 from 1-(3,5-bis-trifluoromethyl-benzoyl)-4-(2-chloro-phenylamino)-piperidine-4-carbonitrile.

Example 68

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(2-methoxy-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 502.2$ ($M+H^+$), was prepared in accordance with the general method of example 63 from 1-(3,5-bis-trifluoromethyl-benzoyl)-4-(2-methoxy-phenylamino)-piperidine-4-carbonitrile.

Example 69

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(4,5-dihydro-1H-imidazol-2-yl-methyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

Ethylenediamine-trimethylaluminium complex (0.8 mmol) was added to a solution of [8-(3,5-bis-trifluoromethyl-benzoyl)-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl]-acetonitrile (0.2 g, 0.4 mmol) in toluene (1.5 mL) and heated to 120 °C for 18 h.

Chromatography on silica gel (dichloromethane/methanol 9:1) yielded the desired product (14 mg, 6 %), MS: $m/e = 554.2$ ($M+H^+$).

Example 70

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-3-methyl-1,3,8-triaza-
5 spiro[4.5]decan-4-one

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (253 mg) was suspended in 1,2-dimethoxyethane (3 mL) and sodium hydride (24 mg, 60 %) was added with stirring at room temperature. After 15 minutes methyl iodide (78 mg) was added and stirring was continued overnight at room temperature. Water was
10 added and the mixture was extracted with ethylacetate. Organic phases were pooled, dried with Na_2SO_4 and the solvent was evaporated. Chromatography on silica gel (hexane/ethylacetate=1:1) yielded the desired product (152 mg, 59%), MS: $m/e = 520.1$ ($M+H^+$).

Example 71

15 3-(1-Benzyl-1H-imidazol-2-ylmethyl)-8-(3,5-bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (253 mg) was suspended in 1,2-dimethoxyethane (3 mL) and sodium hydride (24 mg, 60 %) was added with stirring at room temperature. After 15 minutes 1-benzyl-(2-
20 chloromethyl)-imidazole (121 mg) was added and stirring was continued overnight at 80°C. After cooling down to room temperature water was added and the mixture was extracted with ethylacetate. Organic phases were pooled, dried with Na_2SO_4 and the solvent was evaporated. Chromatography on silica gel (hexane/ethylacetate=1:1) yielded the desired product (215 mg, 64%), MS: $m/e = 676.0$ ($M+H^+$).

25

Example 72

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-3-(2-oxo-oxazolidin-5-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 604.9$ ($M+H^+$), was prepared in accordance with the general method of example 71 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-(2-chloro-
30 phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one and 5-chloromethyl-2-oxazolidinone.

Example 73

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-3-(2-dimethylamino-ethyl)-
1,3,8-triaza-spiro[4.5]decan-4-one

5 The title compound, MS: $m/e = 577.0$ ($M+H^+$), was prepared in accordance with the general method of example 71 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one and 1-chloro-2-dimethylaminoethane hydrochloride.

Example 74

10 8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-3-(2-pyrrolidin-1-yl-ethyl)-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 603.0$ ($M+H^+$), was prepared in accordance with the general method of example 71 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one and 1-(2-chloroethyl)-pyrrolidine hydrochloride.

15 Example 75

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-3-(2-methyl-thiazol-4-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one

20 The title compound, MS: $m/e = 617.0$ ($M+H^+$), was prepared in accordance with the general method of example 71 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one and 4-chloromethyl-2-methylthiazole hydrochloride.

Example 76

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-3-(6-chloro-pyrimidin-4-yl)-
1,3,8-triaza-spiro[4.5]decan-4-one

25 The title compound, MS: $m/e = 618.0$ (100, $M+H^+$), 620.0 (80, $M+H^+$), was prepared in accordance with the general method of example 71 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one and 4,6-dichloropyrimidine.

Example 77

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-3-(3,5-dichloro-pyridin-2-yl)-
1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: m/e = 652.9 (100, M+H⁺), 654.9 (100, M+H⁺), was prepared in
5 accordance with the general method of example 71 from 8-(3,5-bis-trifluoromethyl-
benzoyl)-1-(2-chloro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one and 2,3,5-
trichloropyridine.

Example 78

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-3-(4-trifluoromethyl-pyrimidin-
10 2-yl)-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: m/e = 651.9 (M+H⁺), was prepared in accordance with the
general method of example 71 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-(2-chloro-
phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one and 2-chloro-4-(trifluoromethyl)-pyrimidine.

Example 79

15 8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-3-pyrimidin-2-yl-1,3,8-triaza-
spiro[4.5]decan-4-one

The title compound, MS: m/e = 584.0 (M+H⁺), was prepared in accordance with the
general method of example 71 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-(2-chloro-
phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one and 2-chloro-pyrimidine.

20

Example 80

2-[8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-4-oxo-1,3,8-triaza-
spiro[4.5]dec-3-yl]-N,N-dimethyl-acetamide

The title compound, MS: m/e = 591.0 (M+H⁺), was prepared in accordance with the
general method of example 71 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-(2-chloro-
25 phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one and 2-chloro-N,N-dimethylacetamide.

Example 81

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-3-(3-dimethylamino-propyl)-
1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 591.1$ ($M+H^+$), was prepared in accordance with the general method of example 71 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one and 3-dimethylaminopropylchloride hydrochloride.

5

Example 82

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-3-(3,5-dimethyl-isoxazol-4-yl-methyl)-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 615.1$ ($M+H^+$), was prepared in accordance with the general method of example 71 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one and 4-(chloromethyl)-3,5-dimethylisoxazole.

10

Example 83

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-3-pyridin-3-yl-1,3,8-triaza-spiro[4.5]decan-4-one

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (253 mg) was dissolved in dichloromethane (5 mL), 3-pyridineboronic acid (246mg), triethylamine (101 mg) and copper(II)-acetate (136 mg) were added. The mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was purified by chromatography on silica gel (hexane/ethylacetate=2:1) to yield the desired product (120 mg, 41%), MS: $m/e = 583.0$ ($M+H^+$).

15

20

Example 84

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-3-pyridin-4-yl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 583.0$ ($M+H^+$), was prepared in accordance with the general method of example 83 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one and 4-pyridineboronic acid.

25

Example 85

1-Benzyl-8-(3,5-bis-trifluoromethyl-benzoyl)-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 486.3$ ($M+H^+$), was prepared in accordance with the general method of example 63 from 4-benzylamino-1-(3,5-bis-trifluoromethyl-benzoyl)-piperidine-4-carbonitrile.

30

Example 86

1-Benzyl-8-(3,5-bis-trifluoromethyl-benzoyl)-3-methyl-1,3,8-triaza-spiro[4.5]decan-4-one

- The title compound, MS: $m/e = 500.3$ ($M+H^+$), was prepared in accordance with the
5 general method of example 71 from 1-benzyl-8-(3,5-bis-trifluoromethyl-benzoyl)-1,3,8-triaza-spiro[4.5]decan-4-one and methyl iodide.

Example 87

1-Benzyl-8-(3,5-bis-trifluoromethyl-benzoyl)-3-(2-pyrrolidin-1-yl-ethyl)-1,3,8-triaza-spiro[4.5]decan-4-one hydrochloride

- 10 The title compound, MS: $m/e = 583.2$ ($M+H^+$), was prepared in accordance with the general method of example 71 from 1-benzyl-8-(3,5-bis-trifluoromethyl-benzoyl)-1,3,8-triaza-spiro[4.5]decan-4-one and 1-(2-chloroethyl)-pyrrolidine.

Example 88

15 8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(2-chloro-benzyl)-1,3,8-triaza-spiro[4.5]decan-4-one

1-Benzyl-8-(3,5-bis-trifluoromethyl-benzoyl)-1,3,8-triaza-spiro[4.5]decan-4-one (292 mg) was dissolved in methanol (5 mL) and palladium on charcoal (10%, 78 mg) was added. After stirring in a hydrogen atmosphere (1 bar) at room temperature for 30 min the mixture was filtered over celite and the solvent was evaporated.

- 20 The residue was dissolved in 1,2-dichloroethane (5 ml), 2-chlorobenzaldehyde (71 mg), acetic acid (300 mg) and sodium triacetoxyborohydride (148 mg) were added. The reaction mixture was stirred overnight at room temperature. Water was added, the organic layer was separated and dried. The solvent was evaporated and the residue was purified by chromatography on silica gel (ethylacetate) to yield the desired product (160 mg, 62%),
25 MS: $m/e = 520.1$ ($M+H^+$).

Example 89

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(3-chloro-benzyl)-3-methyl-1,3,8-triaza-spiro[4.5]decan-4-one

- The title compound, MS: $m/e = 534.2$ ($M+H^+$), was prepared in accordance with the
30 general method of example 88 from 1-benzyl-8-(3,5-bis-trifluoromethyl-benzoyl)-3-methyl-1,3,8-triaza-spiro[4.5]decan-4-one and 3-chlorobenzaldehyde.

Example 90

1-Benzoyl-8-(3,5-bis-trifluoromethyl-benzoyl)-1,3,8-triaza-spiro[4.5]decan-4-one

1-Benzyl-8-(3,5-bis-trifluoromethyl-benzoyl)-1,3,8-triaza-spiro[4.5]decan-4-one (50 mg) was dissolved in methanol (2 mL) and palladium on charcoal (10%, 13 mg) was added.

- 5 After stirring in a hydrogen atmosphere (1 bar) at room temperature for 30 min the mixture was filtered over celite and the solvent was evaporated.

The residue was dissolved in dichloromethane (2 mL), triethylamine (22 mg) was added and the mixture was cooled to 0°C. Benzoylchloride (14 mg) was added and the mixture was stirred for 1 h at this temperature. Water was added, the organic layer was separated
10 and dried. The solvent was evaporated and the residue was purified by chromatography on silica gel (ethylacetate) to yield the desired product (30 mg, 60%), MS: $m/e = 500.2$ ($M+H^+$).

Example 91

(rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-2-methyl-1-phenyl-1,3,8-triaza-
15 spiro[4.5]decan-4-one

To a solution of 1-benzyl-piperidin-4-one (18.9 g, 100 mmol) in acetic acid (150 mL) were added at 0°C aniline (10.2 g, 110 mmol) and trimethylsilylcyanide (12.5 mL, 100 mmol). The suspension was stirred for 22 h at room temperature. The reaction mixture was then added to ice-water (350 mL) and ammonia was added until pH 9. After that the mixture
20 was extracted with dichloromethane, the organic phases were pooled, washed with brine and dried with $MgSO_4$. The solvent was evaporated and the residue crystallized from diethylether to yield the intermediate amino nitrile (19.2 g, 66 %).

To a solution of the intermediate amino nitrile (16.0 g, 55 mmol) in formic acid (210 mL) was added with cooling acetic anhydride (210 mL). Stirring continued for 2.5 h at room
25 temperature. Evaporation of the solvent yielded a white foam, which was used without further purification in the next step.

The foam was dissolved in formic acid (210 mL) and acetic acid was added (21 mL). The solution was stirred at room temperature over night. The solvents were evaporated, saturated sodium bicarbonate solution (300 mL) was added and the mixture was extracted
30 with dichloromethane. The organic phases were pooled, dried with Na_2SO_4 and the solvent was evaporated. The residue was a white foam (18.2 g), which was used without further purification in the next step.

The solid was dissolved in triethyl orthoformate (500 mL) and boiled for a week. After cooling the solvent was evaporated to yield 18.5 g brownish foam which was used without further purification in the next step.

5 The brown foam (7.68 g, 24 mmol) was dissolved in THF (80 mL) and was slowly added at room temperature to methylmagnesium bromide (24 mL 3M in diethylether, 72 mmol) and stirred at room temperature overnight. The reaction mixture was quenched with saturated ammonium chloride (100 mL) and extracted with ethyl acetate. Organic phases were pooled and dried with MgSO_4 . Evaporation yielded 7.64 g light brown residue. Chromatography on silica gel (hexane, ethyl acetate, triethyl amine 40:20:1) yielded the
10 intermediate n-benzyl protected piperidine (3.7 g, 46 %).

The intermediate (3.7 g, 11 mmol) was dissolved in methanol (125 mL) and palladium on charcoal (10%, 1.25 g) was added. After stirring in a hydrogen atmosphere (1 bar) at room temperature overnight the mixture was filtered and the solvent was evaporated.

15 The residue was dissolved in dichloromethane (200 mL), triethyl amine (2.1 mL, 15 mmol) and 3,5-bis(trifluoromethyl) benzoylchloride (1.8 mL, 10 mmol) were added and the mixture was stirred at room temperature overnight. Water was added, the organic layer was separated and dried. The solvent was evaporated and the residue was purified by chromatography on silica gel (hexane, ethyl acetate, triethyl amine 20:10:1) to yield the desired product (4.17 g, 86%), MS: $m/e = 486.3$ ($M+H^+$).

20

Example 92

(rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-2-phenethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

25 The title compound, MS: $m/e = 576.0$ ($M+H^+$), was prepared in accordance with the general method of example 91 from 1-benzyl-piperidin-4-one, aniline and phenethyl magnesium chloride.

Example 93

(rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-2-isopropyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

30 The title compound, MS: $m/e = 514.3$ ($M+H^+$), was prepared in accordance with the general method of example 91 from 1-benzyl-piperidin-4-one, aniline and isopropyl magnesium chloride.

Example 94

(rac)-2-Benzyl-8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

5 The title compound, MS: $m/e = 562.2$ ($M+H^+$), was prepared in accordance with the general method of example 91 from 1-benzyl-piperidin-4-one, aniline and benzyl magnesium chloride.

Example 95

(rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-1,2-diphenyl-1,3,8-triaza-spiro[4.5]decan-4-one

10 The title compound, MS: $m/e = 548.1$ ($M+H^+$), was prepared in accordance with the general method of example 91 from 1-benzyl-piperidin-4-one, aniline and phenyl magnesium chloride.

Example 96

15 (rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-2-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 500.2$ ($M+H^+$), was prepared in accordance with the general method of example 91 from 1-benzyl-piperidin-4-one, 1-methyl aniline and methyl magnesium bromide.

Example 97

20 (rac)-2-Benzyl-8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 576.0$ ($M+H^+$), was prepared in accordance with the general method of example 91 from 1-benzyl-piperidin-4-one, 1-methyl aniline and benzyl magnesium chloride.

25

Example 98

(rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-2-phenyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 562.3$ ($M+H^+$), was prepared in accordance with the general method of example 91 from 1-benzyl-piperidin-4-one, 1-methyl aniline and phenyl magnesium chloride.

Example 99

- 5 (rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-2-methyl-1-phenyl-3-pyridin-3-yl-methyl-1,3,8-triaza-spiro[4.5]decan-4-one

(rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-2-methyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one (200 mg, 0.41 mmol) was dissolved in dimethyl formamide (10 mL) and sodium hydride (40 mg, 60% in mineral oil, 1 mmol) and 3-chloromethyl pyridinium
10 chloride (82 mg, .5 mmol) were added and stirred at room temperature overnight. Water (30 mL) was added and the reaction mixture extracted with ethyl acetate. The organic phases were pooled, dried with $MgSO_4$ and the solvent was evaporated. The residue was purified by chromatography on silica gel (ethyl acetate) to yield the desired product (219 mg, 93%), MS: $m/e = 577.0$ ($M+H^+$).

15

Example 100

(rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-2,3-dimethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 500.2$ ($M+H^+$), was prepared in accordance with the general method of example 99 from (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one 1-benzyl-piperidin-4-one and methyl iodide.
20

Example 101

(rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-2-methyl-1-phenyl-3-(2-pyrrolidin-1-yl-ethyl)-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 583.2$ ($M+H^+$), was prepared in accordance with the general method of example 99 from (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one 1-benzyl-piperidin-4-one and 1-(2-chloroethyl)pyrrolidine.
25

Example 102

(rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-2-methyl-3-(2-methyl-thiazol-4-yl-methyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one
30

The title compound, MS: $m/e = 597.0$ ($M+H^+$), was prepared in accordance with the general method of example 99 from (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one 1-benzyl-piperidin-4-one and 4-chloromethyl-2-methylthiazole.

5

Example 103

(rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-3-cyclopropylmethyl-2-methyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 540.3$ ($M+H^+$), was prepared in accordance with the general method of example 99 from (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one 1-benzyl-piperidin-4-one and cyclopropyl methyl bromide.

10

Example 104

(rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(3-dimethylamino-propyl)-2-methyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one

15 The title compound, MS: $m/e = 571.1$ ($M+H^+$), was prepared in accordance with the general method of example 99 from (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one 1-benzyl-piperidin-4-one and 3-dimethylamino-1-propyl chloride.

Example 105

20 (rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-2,3-dimethyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 571.1$ ($M+H^+$), was prepared in accordance with the general method of example 99 from (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one and methyl iodide.

25

Example 106

(rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-2-methyl-3-(2-pyrrolidin-1-yl-ethyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 597.1$ ($M+H^+$), was prepared in accordance with the general method of example 99 from (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one and 1-(2-chloroethyl)-pyrrolidine.

30

Example 107

(rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-2-methyl-3-(2-piperidin-1-yl-ethyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 610.3$ ($M+H^+$), was prepared in accordance with the
5 general method of example 99 from (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one and 1-(2-chloroethyl)-piperidine.

Example 108

(rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-2-methyl-3-(2-piperazin-1-yl-ethyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one

10 The title compound, MS: $m/e = 626.1$ ($M+H^+$), was prepared in accordance with the general method of example 99 from (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one and 1-(2-chloroethyl)-piperazine.

Example 109

15 (rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-2-methyl-1-phenyl-3-pyridin-4-yl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 563.2$ ($M+H^+$), was prepared in accordance with the general method of example 63 from (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one and pyridine-4-boronic acid.

Example 110

20 8-(3,5-Bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione

To a solution of 1-benzyl-piperidin-4-one (18.9 g, 100 mmol) in acetic acid (150 mL) were added at 0°C aniline (10.2 g, 110 mmol) and trimethylsilylcyanide (12.5 mL, 100 mmol). The suspension was stirred for 22 h at room temperature. The reaction mixture was then added to ice-water (350 mL) and ammonia was added until pH 9. After that the mixture
25 was extracted with dichloromethane, the organic phases were pooled, washed with brine and dried with $MgSO_4$. The solvent was evaporated and the residue crystallized from diethylether to yield the intermediate amino nitrile (19.2 g, 66 %).

To a solution of the intermediate amino nitrile (5.0 g, 17.2 mmol) in dichloromethane (50 mL) was added chlorosulfonyl isocyanate (1.65 mL, 19 mmol). Stirring continued for 1 h
30 at room temperature. Evaporation of the solvent yielded a white solid, which was used without further purification in the next step.

The white solid was suspended in 1N hydrochloric acid (50 mL) and refluxed for 2 h. The pH was adjusted to exactly 7 by adding 15% sodium hydroxide solution and the mixture was then extracted with dichloromethane. Organic phases were pooled and dried with MgSO_4 . Evaporation yielded 5.4 g of a solid residue. Chromatography on silica gel (hexane, ethyl acetate 1:1) yielded the intermediate n-benzyl protected spiropiperidine (2.6 g, 45 %).

The intermediate (500 mg, 1.5 mmol) was dissolved in methanol (30 mL) and palladium on charcoal (10%, 100 mg) and 5 drops of concentrated hydrochloric acid were added. After stirring in a hydrogen atmosphere (1 bar) at room temperature overnight the mixture was filtered and the solvent was evaporated.

The residue was dissolved in dichloromethane (20 mL), triethyl amine (0.63 mL, 4.5 mmol) and 3,5-bis(trifluoromethyl) benzoylchloride (0.27 mL, 1.5 mmol) were added and the mixture was stirred at room temperature overnight. Water was added, the organic layer was separated and dried. The solvent was evaporated and the residue was purified by chromatography on silica gel (hexane, ethyl acetate 1:1) to yield the desired product (414 mg, 57%), MS: $m/e = 486.3$ ($M+H^+$).

Example 111

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione

The title compound, MS: $m/e = 498.3$ ($M-H^+$), was prepared in accordance with the general method of example 110 from 1-benzyl-piperidin-4-one and o-toluidine.

Example 112

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-phenyl-3-pyridin-3-yl-methyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione

The title compound, MS: $m/e = 577.0$ ($M+H^+$), was prepared in accordance with the general method of example 121 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione and 3-(hydroxymethyl)-pyridine.

Example 113

8-(3,5-Bis-trifluoromethyl-benzoyl)-1,3-diphenyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione

The title compound, MS: $m/e = 562.2$ ($M+H^+$), was prepared in accordance with the general method of example 110 from 1-benzyl-piperidin-4-one, aniline and phenyl isocyanate.

Example 114

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-pyridin-3-yl-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione

- 5 The title compound, MS: $m/e = 591.1$ ($M+H^+$), was prepared in accordance with the general method of example 121 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione and 3-(hydroxymethyl)-pyridine.

Example 115

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(2-pyrrolidin-1-yl-ethyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione

- 10 The title compound, MS: $m/e = 597.1$ ($M+H^+$), was prepared in accordance with the general method of example 99 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione and 1-(2-chloroethyl)-pyrrolidine.

Example 116

- 15 8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(3,5-dimethyl-isoxazol-4-yl-methyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione

The title compound, MS: $m/e = 609.0$ ($M+H^+$), was prepared in accordance with the general method of example 99 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione and 4-(chloromethyl)-3,5-dimethylisoxazole.

Example 117

- 20 3-(1H-Benzoimidazol-2-yl-methyl)-8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione

The title compound, MS: $m/e = 630.0$ ($M+H^+$), was prepared in accordance with the general method of example 99 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione and 2-(chloromethyl)-benzimidazole.

25

Example 118

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(2-methyl-thiazol-4-yl-methyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione

The title compound, MS: $m/e = 611.0$ ($M+H^+$), was prepared in accordance with the general method of example 99 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione and 4-chloromethyl-2-methylthiazole.

Example 119

- 5 8-(3,5-Bis-trifluoromethyl-benzoyl)-3-[1,2,4]oxadiazol-3-yl-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione

The title compound, MS: $m/e = 581.2$ (M^+), was prepared in accordance with the general method of example 99 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione and 3-(chloromethyl)-1,2,4-oxadiazole.

- 10 Example 120

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(2-oxo-oxazolidin-5-yl-methyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione

- The title compound, MS: $m/e = 599.0$ (M^+), was prepared in accordance with the general method of example 99 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione and 5-chloromethyl-2-oxazolidinone.
- 15

Example 121

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-furan-2-yl-methyl-1-phenyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione

- 8-(3,5-Bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione
(200 mg, 0.41 mmol) was dissolved in dry dioxane (10 mL) and triphenylphosphin (145 mg, 0.54 mmol), furfuryl alcohol (53.1 mg, 0.54 mmol) and diethylazodicarboxylate (40% in toluene, 0.54 mmol) were added sequentially and stirred at room temperature overnight. The solvent was evaporated and the residue was purified by chromatography on silica gel (dichloromethane) to yield the desired product (143 mg, 61%), MS: $m/e = 566.1$
($M+H^+$).
- 20
- 25

Example 122

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-furan-3-yl-methyl-1-phenyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione

- The title compound, MS: $m/e = 566.1$ (M^+), was prepared in accordance with the general method of example 121 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione and 3-furane methanol.
- 30

Example 123

(S)-8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(5-oxo-pyrrolidin-2-yl-methyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione

5 The title compound, MS: $m/e = 583.1 (M^+)$, was prepared in accordance with the general method of example 121 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione and (S)-5-(hydroxymethyl)-2-pyrrolidinone.

Example 124

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(5-methyl-isoxazol-3-yl-methyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione

10 The title compound, MS: $m/e = 595.0 (M^+)$, was prepared in accordance with the general method of example 121 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione and 5-methylisoxazole-3-methanol.

Example 125

15 8-(3,5-Bis-trifluoromethyl-benzoyl)-3-furan-3-yl-ethyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione

The title compound, MS: $m/e = 580.1 (M^+)$, was prepared in accordance with the general method of example 121 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione and 3-furane-methanol.

Example 126

20 8-(3,5-Bis-trifluoromethyl-benzoyl)-3-furan-2-yl-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione

The title compound, MS: $m/e = 580.0 (M^+)$, was prepared in accordance with the general method of example 121 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione and furfuryl alcohol.

25

Example 127

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-thiophen-2-yl-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione

The title compound, MS: $m/e = 596.0$ (M^+), was prepared in accordance with the general method of example 121 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione and 2-thiophene methanol.

Example 128

- 5 8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(2-morpholin-4-yl-ethyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione

The title compound, MS: $m/e = 613.1$ (M^+), was prepared in accordance with the general method of example 121 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione and N-(2-hydroxyethyl)morpholine.

10

Example 129

8-(3,5-Bis-trifluoromethyl-benzoyl)-4-hydroxy-1,3-diphenyl-1,3,8-triaza-spiro[4.5]decan-2-one

To a solution of 1-benzyl-piperidin-4-one (18.9 g, 100 mmol) in acetic acid (150 mL) were added at 0°C aniline (10.2 g, 110 mmol) and trimethylsilylcyanide (12.5 mL, 100 mmol).

- 15 The suspension was stirred for 22 h at room temperature. The reaction mixture was then added to ice-water (350 mL) and ammonia was added until pH 9. After that the mixture was extracted with dichloromethane, the organic phases were pooled, washed with brine and dried with $MgSO_4$. The solvent was evaporated and the residue crystallized from diethylether to yield the intermediate amino nitrile (19.2 g, 66 %).

- 20 To a solution of the intermediate amino nitrile (5.0 g, 17.2 mmol) in dichloromethane (50 mL) was added phenyl isocyanate (2.20 mL, 20 mmol). Stirring continued for 1 h at room temperature. Evaporation of the solvent yielded a white solid, which was used without further purification in the next step.

- 25 The white solid was suspended in 1N hydrochloric acid (50 mL) and refluxed for 2 h. The pH was adjusted to exactly 7 by adding 15% sodium hydroxide solution and the mixture was then extracted with dichloromethane. Organic phases were pooled, dried with $MgSO_4$ and evaporated. Chromatography on silica gel (hexane, ethyl acetate 1:1) yielded the intermediate n-benzyl protected spiropiperidine (5.54 g, 78 %).

- 30 The n-benzyl protected spiropiperidine (4.0 g, 9.7 mmol) was dissolved in tetrahydrofuran (50 mL) and diisobutyl aluminium hydride (24 mL, 1M in THF) were added at 0°C. The reaction mixture was stirred at room temperature overnight and the solvent was evaporated. Chromatography of the residue on silica gel (hexane, ethyl acetate, triethyl amine 40:10:1) gave the reduced intermediate (874 mg, 22%).

The intermediate (870 mg, 2.1 mmol) was dissolved in methanol (30 mL) and palladium on charcoal (10%, 200 mg) and 5 drops of concentrated hydrochloric acid were added. After stirring in a hydrogen atmosphere (1 bar) at room temperature overnight the mixture was filtered and the solvent was evaporated.

- 5 The residue was dissolved in dichloromethane (20 ml), triethyl amine (1.2 mL, 8.5 mmol) and 3,5-bis(trifluoromethyl) benzoylchloride (0.42 mL, 2.3 mmol) were added and the mixture was stirred at room temperature overnight. Water was added, the organic layer was separated and dried. The solvent was evaporated and the residue was purified by chromatography on silica gel (hexane, ethyl acetate 1:1) to yield the desired product (497
10 mg, 42%), MS: $m/e = 564.1$ ($M+H^+$).

Example 130

8-(3,5-Bis-trifluoromethyl-benzoyl)-4-methoxy-1,3-diphenyl-1,3,8-triaza-spiro[4.5]decan-2-one

The title compound, MS: $m/e = 578:0$ (M^+), was obtained as a byproduct of example 129.

15

Example 131

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-2-one

- To a solution of 1-benzyl-piperidin-4-one (37.8 g, 200 mmol) in acetic acid (300 mL) were added at 0°C o-toluidine (23.8 g, 220 mmol) and trimethylsilylcyanide (25.0 mL, 200
20 mmol). The suspension was stirred for 22 h at room temperature. The reaction mixture was then added to ice-water (500 mL) and ammonia was added until pH 9. After that the mixture was extracted with dichloromethane, the organic phases were pooled, washed with brine and dried with $MgSO_4$. The solvent was evaporated and the residue crystallized from diethylether to yield the intermediate amino nitrile (46.2 g, 75 %).

- The intermediate amino nitrile (29.5 g, 96 mmol) was dissolved in acetic acid (200 mL),
25 PtO_2 (1.3 g, 5.7 mmol) was added and the reaction mixture was hydrogenated at 2.7 bar at room temperature for 3 days. Acetic acid was evaporated and the residue was treated with saturated sodium bicarbonate solution until pH 9. The mixture was then extracted with dichloromethane. Organic phases were pooled and dried with $MgSO_4$. Evaporation yielded 21.2 g (71%) of an oil.

- 30 To a solution of the intermediate triamine (3.2g, 10.2 mmol) in dichloromethane (330 mL) and triethylamine (2.9 mL, 20.5 mmol) was added at -20°C trichloromethyl chloroformat (0.446 mL, 3.6 mmol) in dichloromethane (30 mL). The reaction mixture was then stirred at room temperature overnight. Water (50 mL) was added and the mixture was extracted

with dichloromethane. Organic phases were pooled and dried with MgSO_4 . Evaporation and chromatography on silica gel (dichloromethane/methanol 99:1) yielded the intermediate N-benzyl protected spiropiperidine (1.4g, 41%).

5 The intermediate N-benzyl protected spiropiperidine (3.05g, 9.1 mmol) was dissolved in methanol (120 mL) and palladium on charcoal (10%, 610 mg) and 20 drops of concentrated hydrochloric acid were added. After stirring in a hydrogen atmosphere (1 bar) at room temperature overnight the mixture was filtered and the solvent was evaporated.

10 The residue was dissolved in dichloromethane (100 ml), triethyl amine (3.73 mL, 26.6 mmol) and 3,5-bis(trifluoromethyl) benzoylchloride (2.45 mL, 8.9 mmol) were added and the mixture was stirred at room temperature overnight. Water was added, the organic layer was separated and dried. The solvent was evaporated and the recrystallized from dichloromethane to yield the desired product as white crystals (3.29 g, 76%), MS: $m/e = 486.3$ ($M+H^+$).

15

Example 132

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(2-pyrrolidin-1-yl-ethyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-2-one

20 The title compound, MS: $m/e = 583.2$ ($M+H^+$), was prepared in accordance with the general method of example 99 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-2-one and 1-(2-chloroethyl)-pyrrolidine.

Example 133

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one

25 The title compound, MS: $m/e = 500.2$ ($M+H^+$), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one and iodomethane in 1,2-dimethoxyethane as solvent.

Example 134

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(2-methyl-thiazol-4-yl-methyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one

30 The title compound, MS: $m/e = 597.0$ ($M+H^+$), was prepared in accordance with the general method of example 4 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-

triazaspiro[4.5]decan-4-one and 4-chloromethyl-2-methyl-thiazole in 1,2-dimethoxyethane as solvent.

Example 135

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-1,3,8-triazaspiro[4.5]decane-
5 2,4-dione

To a solution of 1-(3,5-bis-trifluoromethyl-benzoyl)-4-(2-chloro-phenylamino)-piperidine-4-carbonitrile (5.0 g, 10.5 mmol) in dichloromethane (50 mL) was added chlorosulfonyl isocyanate (1 mL, 11.5 mmol). Stirring continued for 1 h at room temperature. Evaporation of the solvent yielded a white foam, which was used without
10 further purification in the next step.

The white foam was suspended in 1N hydrochloric acid (50 mL) and refluxed for 2 h. The obtained suspension was filtered to yield 5.4 g of a solid residue. Chromatography on silica gel (hexane, ethyl acetate 2:1) and recrystallization from ethyl acetate/n-hexane yielded the desired product (2.9 g, 53%), mp 153-154°C, MS: m/e = 520.1 (M+H⁺).

15

Example 136

Rac-8-(3,5-Bis-trifluoromethyl-benzoyl)-2-methyl-3-phenyl-1-o-tolyl-1,3,8-triazaspiro[4.5]decan-4-one

The title compound, MS: m/e = 576.0 (M+H⁺), was prepared in accordance with the general method of example 62 from (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-1-o-tolyl-1,3,8-triazaspiro[4.5]decan-4-one and 4 phenylboronic acid.
20

Example 137

Rac-8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(2-methoxy-ethyl)-2-methyl-1-o-tolyl-1,3,8-triazaspiro[4.5]decan-4-one

The title compound, MS: m/e = 542.2 (M+H⁺), was prepared in accordance with the general method of example 99 from (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-1-o-tolyl-1,3,8-triazaspiro[4.5]decan-4-one and 2-chloroethyl-methyl ether.
25

Example 138

Rac-8-(3,5-Bis-trifluoromethyl-benzoyl)-3-cyclopropylmethyl-2-methyl-1-o-tolyl-1,3,8-triazaspiro[4.5]decan-4-one

The title compound, MS: $m/e = 554.2$ ($M+H^+$), was prepared in accordance with the general method of example 99 from (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one and cyclopropyl methyl bromide.

Example 139

- 5 Rac-8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(2,2-difluoro-ethyl)-2-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 564.2$ ($M+H^+$), was prepared in accordance with the general method of example 99 from (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one and 2,2-difluoroethyl bromide.

10

Example 140

Rac-8-(3,5-Bis-trifluoromethyl-benzoyl)-2-methyl-3-(3-methyl-but-2-enyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one

- The title compound, MS: $m/e = 568.2$ ($M+H^+$), was prepared in accordance with the general method of example 99 from (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one and 1-bromo-3-methyl-2-butene.

Example 141

Rac-8-(3,5-Bis-trifluoromethyl-benzoyl)-2-methyl-3-(2-morpholin-4-yl-ethyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one

- The title compound, MS: $m/e = 613.2$ ($M+H^+$), was prepared in accordance with the general method of example 99 from (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one and 4-(chloroethyl)morpholine.

Example 142

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(1-methyl-1H-imidazol-2-yl-methyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one

- 25 The title compound, MS: $m/e = 580.3$ ($M+H^+$), was prepared in accordance with the general method of example 99 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one and 2-chloromethyl-1-methyl-1H-imidazole.

Example 143

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-3-(1-methyl-1H-imidazol-2-ylmethyl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione

5 The title compound, MS: $m/e = 614.1$ ($M+H^+$), was prepared in accordance with the general method of example 121 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione and 1-methylimidazole-2-methanol.

Example 144

8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-3-(1,5-dimethyl-1H-pyrazol-3-ylmethyl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione

10 The title compound, MS: $m/e = 627.1$ (M^+), was prepared in accordance with the general method of example 121 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione and 1,5-dimethylpyrazole-3-methanol.

Example 145

15 8-(3,5-Bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-3-(1,5-dimethyl-1H-pyrazol-3-ylmethyl)-1,3,8-triaza-spiro[4.5]decane-2,4-dione

The title compound, MS: $m/e = 585.1$ (M^+), was prepared in accordance with the general method of example 121 from 8-(3,5-bis-trifluoromethyl-benzoyl)-3-(3-dimethylamino-propyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione and 3-dimethylamino-1-propyl chloride.

20

Example 146

(rac)-8-(3,5-Dimethoxy-benzoyl)-2-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 424.5$ ($M+H^+$), was prepared in accordance with the general method of example 91 from 1-benzyl-piperidin-4-one, 1-methyl aniline, methyl magnesium bromide and 3,5-dimethoxy benzoyl chloride.

25

Example 147

(rac)-8-(3,5-Dichloro-benzoyl)-2-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one

The title compound, MS: $m/e = 432.4$ ($M+H^+$), was prepared in accordance with the general method of example 91 from 1-benzyl-piperidin-4-one, 1-methyl aniline, methyl magnesium bromide and 3,5-dichloro benzoyl chloride.

Example 148

(rac)-8-(3-Fluoro-5-trifluoromethyl-benzoyl)-2-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one

- 5 The title compound, MS: $m/e = 450.4$ ($M+H^+$), was prepared in accordance with the general method of example 91 from 1-benzyl-piperidin-4-one, 1-methyl aniline, methyl magnesium bromide and 3-fluoro-5-trifluoromethyl-benzoyl chloride.

Example 149

(rac)-8-(3,5-Difluoro-benzoyl)-2-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one

- 10 The title compound, MS: $m/e = 400.5$ ($M+H^+$), was prepared in accordance with the general method of example 91 from 1-benzyl-piperidin-4-one, 1-methyl aniline, methyl magnesium bromide and 3,5-difluoro-benzoyl chloride.

Example 150

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-cyclopropylmethyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-2-one

- 15 The title compound, MS: $m/e = 540.4$ ($M+H^+$), was prepared in accordance with the general method of example 99 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-2-one and cyclopropyl methyl bromide.

Example 151

20 8-(3,5-Bis-trifluoromethyl-benzoyl)-3-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-2-one

The title compound, MS: $m/e = 500.2$ ($M+H^+$), was prepared in accordance with the general method of example 99 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-2-one and methyl iodide.

Example 152

25 8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(2-morpholin-4-yl-ethyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-2-one

The title compound, MS: $m/e = 599.1$ ($M+H^+$), was prepared in accordance with the general method of example 99 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-2-one and 4-(chloroethyl)morpholine.

Example 153

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(2-methoxy-ethyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-2-one

- The title compound, MS: $m/e = 544.2$ ($M+H^+$), was prepared in accordance with the
5 general method of example 99 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-2-one and 2-chloromethyl methyl ether.

Example 154

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(3-dimethylamino-propyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-2-one

- 10 The title compound, MS: $m/e = 571.1$ ($M+H^+$), was prepared in accordance with the general method of example 99 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-2-one and 3-dimethylamino-1-propyl chloride.

Example 155

3-Acetyl-8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-2-one

- 15 The title compound, MS: $m/e = 528.1$ ($M+H^+$), was prepared in accordance with the general method of example 99 from 8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-2-one and acetyl chloride.

Example 156

(rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-4-phenyl-2,8-diaza-spiro[4.5]decane-1,3-dione

- 20 To a solution sodium ethoxide (prepared by slow addition of 22 g, 0.96 mol Na to dry 800 mL ethanol) was added benzyl cyanide (113 g, 1.05 mol) and N-benzyl-4-piperidone (90 g, 0.48 mol) at room temperature. The reaction mixture was stirred at 85°C for 3 h and the solvent was evaporated. The residue was poured into a mixture of ice (1 kg) and concentrated hydrochloric acid (200 mL). The pH was then adjusted to 9 addition of solid
25 sodium hydroxide and the mixture was extracted three times with ethyl acetate (500 mL each). Organic phases were pooled and dried with $MgSO_4$. The solvent was evaporated and chromatography on silica gel (hexane, ethyl acetate, triethyl amine 80:20:1) gave (1-benzyl-piperidin-4-ylidene)-phenyl-acetonitrile as yellow crystals (135 g, 97%).

- To a solution of the intermediate (1-benzyl-piperidin-4-ylidene)-phenyl-acetonitrile (135
30 g, 0.47 mol) in ethanol (400 mL) was added potassium cyanide (30 g, 0.47 mol) in water (80 mL). Stirring continued at 90°C overnight. The solvent was evaporated. The residue

was taken up in 2N hydrochloric acid (300 mL) and concentrated hydrochloric acid (50 mL) was added to adjust at pH 1-2. The reaction mixture was stirred at reflux overnight. After cooling to room temperature solid sodium carbonate until pH 8-9 was added and the mixture was extracted three times with methylene chloride (300 mL each). Organic phases
5 were pooled, dried with MgSO_4 and evaporated. The crude product was suspended in ethyl acetate (300 mL) and left at room temperature overnight. The crystals were filtered off and dried to give 106 g (68%) of the intermediate (rac)-8-benzyl-4-phenyl-2,8-diaza-spiro[4.5]decane-1,3-dione.

The intermediate (rac)-8-benzyl-4-phenyl-2,8-diaza-spiro[4.5]decane-1,3-dione (4.0 g, 12
10 mmol) was dissolved in methanol (100 mL) and concentrated hydrochloric acid (1 mL) and palladium on charcoal (10%, 0.60 g) were added. After stirring in a hydrogen atmosphere (1 bar) at room temperature overnight the mixture was filtered and the solvent was evaporated.

The residue was dissolved in dichloromethane (100 mL), triethyl amine (5.5 mL, 40 mmol)
15 and 3,5-bis(trifluoromethyl) benzoylchloride (2.7 mL, 15 mmol) were added and the mixture was stirred at room temperature overnight. Water was added, the organic layer was separated and dried. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (hexane, ethyl acetate, triethyl amine 30:10:1) to yield the desired product (3.44 g, 59%), MS: $m/e = 485.3$ ($M+H^+$).

20

Example 157

(rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-2-methyl-4-phenyl-2,8-diaza-spiro[4.5]decane-1,3-dione

The title compound, MS: $m/e = 499.2$ ($M+H^+$), was prepared in accordance with the general method of example 121 from (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-4-phenyl-
25 2,8-diaza-spiro[4.5]decane-1,3-dione and methyl iodide.

Example 158

(rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-2-(2-morpholin-4-yl-ethyl)-4-phenyl-2,8-diaza-spiro[4.5]decane-1,3-dione

The title compound, MS: $m/e = 598.1$ ($M+H^+$), was prepared in accordance with the
30 general method of example 121 from (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-4-phenyl-2,8-diaza-spiro[4.5]decane-1,3-dione and N-(2-hydroxyethyl)-morpholine.

Example 159

(rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-4-phenyl-2-(2-pyrrolidin-1-yl-ethyl)-2,8-diaza-spiro[4.5]decane-1,3-dione

- 5 The title compound, MS: $m/e = 582.2$ ($M+H^+$), was prepared in accordance with the general method of example 121 from (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-4-phenyl-2,8-diaza-spiro[4.5]decane-1,3-dione and 1-(2-hydroxyethyl)-pyrrolidine.

Example 160

(rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-2-(3-dimethylamino-propyl)-4-phenyl-2,8-diaza-spiro[4.5]decane-1,3-dione

- 10 The title compound, MS: $m/e = 570.2$ ($M+H^+$), was prepared in accordance with the general method of example 121 from (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-4-phenyl-2,8-diaza-spiro[4.5]decane-1,3-dione and 3-dimethylamino-1-propanol.

Example 161

(rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one

- 15 (rac)-8-Benzyl-4-phenyl-2,8-diaza-spiro[4.5]decane-1,3-dione (10.0 g, 30 mmol, synthesis described in example 156) was dissolved in toluene (200 mL). Diisobutyl aluminium hydride (220 mL, 1M in THF, 220 mmol) was slowly added while cooling with an ice bath so that the reaction temperature did not exceed 10°C. The reaction mixture was stirred at room temperature for 2 days. A mixture of methanol (6 mL) and water (6 mL) was added at room temperature. The resulting gel was filtered through dicalit and washed with
20 methylene chloride. The filtrate was evaporated to give 8-benzyl-3-hydroxy-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one as a mixture of diastereomers (8.0 g, 80%).

- The intermediate 8-benzyl-3-hydroxy-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one (8.0 g, 23.8 mmol) was dissolved in glacial acetic acid (50 mL) and refluxed for 1.5 h. The reaction
25 mixture was poured into ice water (500 mL) and adjusted to pH 8-9 by addition of solid sodium hydroxide. The mixture was extracted three times with ethyl acetate (300 mL each). Organic phases were pooled, dried with magnesium sulfate and evaporated. The crude product was recrystallized from methylene chloride to give 8-benzyl-4-phenyl-2,8-diaza-spiro[4.5]dec-3-en-1-one as white crystals (2.64 g, 35 %).

- 30 The intermediate 8-benzyl-4-phenyl-2,8-diaza-spiro[4.5]dec-3-en-1-one (3.7 g, 11.6 mmol) was dissolved in methanol (100 mL) and concentrated hydrochloric acid (1 mL) and palladium on charcoal (10 %, 0.60 g) were added. After stirring in a hydrogen

atmosphere (1 bar) at room temperature overnight the mixture was filtered and the solvent was evaporated.

The residue was dissolved in dichloromethane (100 ml), triethyl amine (8.1 mL, 58 mmol) and 3,5-bis(trifluoromethyl) benzoylchloride (2.65 mL, 15 mmol) were added and the
5 mixture was stirred at room temperature overnight. Water was added, the organic layer was separated and dried. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (methylene chloride/methanol 98:2) to yield the desired product (4.65 g, 85%), MS: $m/e = 471.2$ ($M+H^+$).

Example 162

10 (rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-2-methyl-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one

The title compound, MS: $m/e = 485.3$ ($M+H^+$), was prepared in accordance with the general method of example 99 from (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one and methyl iodide.

15

Example 163

(rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-4-phenyl-2-(2-pyrrolidin-1-yl-ethyl)-2,8-diaza-spiro[4.5]decan-1-one

The title compound, MS: $m/e = 568.3$ ($M+H^+$), was prepared in accordance with the general method of example 99 from (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-4-phenyl-
20 2,8-diaza-spiro[4.5]decan-1-one and 1-(2-chloroethyl)-pyrrolidine.

Example 164

(rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-2-(2-methoxy-ethyl)-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one

The title compound, MS: $m/e = 529.2$ ($M+H^+$), was prepared in accordance with the
25 general method of example 99 from (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one and 2-chloroethyl-methyl-ether.

Example 165

(rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-2-(2-morpholin-4-yl-ethyl)-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one

The title compound, MS: $m/e = 584.1$ ($M+H^+$), was prepared in accordance with the general method of example 99 from (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one and 4-(2-chloroethyl)-morpholine.

Example 166

- 5 (rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-2-(3-dimethylamino-propyl)-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one

The title compound, MS: $m/e = 556.2$ ($M+H^+$), was prepared in accordance with the general method of example 99 from (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one and 3-dimethylamino-1-propyl chloride.

10

Example 167

(rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-4-phenyl-2-pyridin-3-yl-methyl-2,8-diaza-spiro[4.5]decan-1-one

- The title compound, MS: $m/e = 562.3$ ($M+H^+$), was prepared in accordance with the general method of example 99 from (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one and 3-(chloromethyl)pyridine.

15

Example 168

(rac)-(3,5-Bis-trifluoromethyl-phenyl)-(2-methyl-4-phenyl-2,8-diaza-spiro[4.5]dec-8-yl)-methanone

- (rac)-8-Benzyl-4-phenyl-2,8-diaza-spiro[4.5]decane-1,3-dion (3.0 g, 9.0 mmol, synthesis described in example 156) was dissolved in dry tetrahydrofuran (50 mL) and triphenylphosphin (3.1 g, 11.7 mmol), methanol (0.374 g, 11.7 mmol) and diethylazodicarboxylate (5.35 mL, 40% in toluene, 11.7 mmol) were added sequentially and stirred at room temperature overnight. The solvent was evaporated and the residue was purified by chromatography on silica gel (dichloromethane/methanol/triethyl amine 20 98:1:1) to yield the intermediate (rac)-8-benzyl-2-methyl-4-phenyl-2,8-diaza-spiro[4.5]decane-1,3-dion (2.57g, 82 %).

- Lithium aluminium hydride (1.39 g, 37 mmol) was dissolved in tetrahydrofuran (20 mL) and the intermediate (rac)-8-benzyl-2-methyl-4-phenyl-2,8-diaza-spiro[4.5]decane-1,3-dion (2.55 g, 7.32 mmol, dissolved in 20 mL dry tetrahydrofuran) was added slowly. The reaction mixture was stirred at room temperature for 2 h. Water (1.4 mL), sodium 30 hydroxide (15% in water, 1.5 mL) and water (4.2 mL) were added dropwise. The precipitate was filtered off and the filtrate was evaporated. The residue was purified by flash

chromatography (hexane/ethyl acetate/triethyl amine 30:20:1) to yield the intermediate (rac)-8-benzyl-2-methyl-4-phenyl-2,8-diaza-spiro[4.5]decane (1.40 g, 60 %).

The intermediate (rac)-8-benzyl-2-methyl-4-phenyl-2,8-diaza-spiro[4.5]decane (1.29 g, 2.51 mmol) was dissolved in methanol (50 mL) and concentrated hydrochloric acid (0.3 mL) and palladium on charcoal (10 %, 0.214 g) were added. After stirring in a hydrogen atmosphere (1 bar) at room temperature overnight the mixture was filtered and the solvent was evaporated.

The residue was dissolved in dichloromethane (50 mL), triethyl amine (2.04 mL, 20 mmol) and 3,5-bis(trifluoromethyl) benzoylchloride (0.95 mL, 5.2 mmol) were added and the mixture was stirred at room temperature overnight. Water was added, the organic layer was separated and dried. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (hexane/ethyl acetate/triethyl amine 10:20:1) to yield the desired product (1.18 g, 62 %), MS: $m/e = 471.2$ ($M+H^+$).

Example 169

8-(3,5-Bis-trifluoromethyl-benzoyl)-4-o-tolyl-2,8-diaza-spiro[4.5]dec-3-en-1-one

The title compound, MS: $m/e = 483.1$ ($M+H^+$), was prepared in accordance with the general methods of example 156 and 161 from o-tolyl cyanide and N-benzyl-4-piperidone. Reduction of the double bond with hydrogen was not successful and the 2,8-diaza-spiro[4.5]dec-3-en-1-one core was obtained instead of the 2,8-diaza-spiro[4.5]decan-1-one core.

Example 170

8-(3,5-Bis-trifluoromethyl-benzoyl)-2-methyl-4-o-tolyl-2,8-diaza-spiro[4.5]dec-3-en-1-one

The title compound, MS: $m/e = 497.1$ ($M+H^+$), was prepared in accordance with the general method of example 99 from 8-(3,5-bis-trifluoromethyl-benzoyl)-4-o-tolyl-2,8-diaza-spiro[4.5]dec-3-en-1-one and methyl iodide.

Example 171

8-(3,5-Bis-trifluoromethyl-benzoyl)-2-cyclopropylmethyl-4-o-tolyl-2,8-diaza-spiro[4.5]dec-3-en-1-one

The title compound, MS: $m/e = 537.2$ ($M+H^+$), was prepared in accordance with the general method of example 99 from 8-(3,5-bis-trifluoromethyl-benzoyl)-4-o-tolyl-2,8-diaza-spiro[4.5]dec-3-en-1-one and cyclopropyl methyl bromide.

Example 172

5 8-(3,5-Bis-trifluoromethyl-benzoyl)-2-(2-pyrrolidin-1-yl-ethyl)-4-o-tolyl-2,8-diaza-spiro[4.5]dec-3-en-1-one

The title compound, MS: $m/e = 580.1$ ($M+H^+$), was prepared in accordance with the general method of example 99 from 8-(3,5-bis-trifluoromethyl-benzoyl)-4-o-tolyl-2,8-diaza-spiro[4.5]dec-3-en-1-one and 1-(2-chloroethyl)-pyrrolidine.

10

Example 173

8-(3,5-Bis-trifluoromethyl-benzoyl)-2-(2-morpholin-4-yl-ethyl)-4-o-tolyl-2,8-diaza-spiro[4.5]dec-3-en-1-one

The title compound, MS: $m/e = 596.1$ ($M+H^+$), was prepared in accordance with the general method of example 99 from 8-(3,5-bis-trifluoromethyl-benzoyl)-4-o-tolyl-2,8-diaza-spiro[4.5]dec-3-en-1-one and 1-(2-chloroethyl)-morpholine.

15

Example 174

8-(3,5-Bis-trifluoromethyl-benzoyl)-2-(3-dimethylamino-propyl)-4-o-tolyl-2,8-diaza-spiro[4.5]dec-3-en-1-one

The title compound, MS: $m/e = 568.2$ ($M+H^+$), was prepared in accordance with the general method of example 99 from 8-(3,5-bis-trifluoromethyl-benzoyl)-4-o-tolyl-2,8-diaza-spiro[4.5]dec-3-en-1-one and 3-dimethylamino-1-propyl chloride.

20

Example 175

8-(3,5-Bis-trifluoromethyl-benzoyl)-2-pyridin-3-yl-methyl-4-o-tolyl-2,8-diaza-spiro[4.5]dec-3-en-1-one

25 The title compound, MS: $m/e = 574.1$ ($M+H^+$), was prepared in accordance with the general method of example 99 from 8-(3,5-bis-trifluoromethyl-benzoyl)-4-o-tolyl-2,8-diaza-spiro[4.5]dec-3-en-1-one and 3-chloromethyl pyridine.

Example 176

(rac)-8-(3,5-Bis-trifluoromethyl-benzoyl)-4-o-tolyl-2,8-diaza-spiro[4.5]decan-1-one

The title compound, MS: $m/e = 485.3$ ($M+H^+$), was prepared in accordance with the general methods of example 156 and 161 from *o*-tolyl cyanide and *N*-benzyl-4-piperidone. Reduction with hydrogen was performed for three days to also reduce the double bond.

Example A

5 1-(3,5-Bis-trifluoromethyl-benzoyl)-piperidin-4-one

A solution of 3,5-bis-trifluoromethyl-benzoyl chloride (17.4 g, 63 mmol) in dichloromethane (30 mL) was added with cooling to a solution of 4-piperidone trifluoroacetate (13.4 g, 63 mmol) and triethylamine (22 mL, 158 mmol) so that the temperature did not rise above 20 °C. Stirring continued for 2 h at room temperature.

- 10 Water was added, the phases were separated and the water phase was extracted with dichloromethane. The organic phases were pooled, dried with $MgSO_4$ and the solvent was evaporated. Chromatography on silica gel (ethyl acetate/*n*-hexane 1:1) yielded the desired product (20.2 g, 94 %), m.p. 155-157 °C and MS: $m/e = 339.1$ (M^+).

Example B

15 1-(3,5-Bis-trifluoromethyl-benzoyl)-4-(3-chloro-phenylamino)-piperidine-4-carbonitrile

To a solution of 1-(3,5-bis-trifluoromethyl-benzoyl)-piperidin-4-one (5.1 g, 15 mmol) in acetic acid (20 mL) were added with cooling 3-chloroaniline (1.7 mL, 16.5 mmol) and trimethylsilylcyanide (1.9 mL, 15 mmol) so that the temperature did not rise above 20 °C. The suspension was stirred for 6 h at room temperature. The reaction mixture was then
20 added to ice-water (350 mL), ammonia (55 mL, 25%) was added to the mixture which was stirred for 15 min. After that the mixture was extracted with dichloromethane, the organic phases were pooled, washed with brine and dried with $MgSO_4$. The solvent was evaporated and the residue crystallized from ethylacetate to yield the desired product (5.3 g, 74 %), m.p. 205-207 °C and MS: $m/e = 476.1$ ($M+H^+$).

Example C

25 1-(3,5-Bis-trifluoromethyl-benzoyl)-4-(4-chloro-phenylamino)-piperidine-4-carbonitrile

The title compound, m.p. 176-180 °C and MS: $m/e = 474.1$ ($M-H^-$), was prepared in accordance with the general method of example B from 1-(3,5-bis-trifluoromethyl-benzoyl)-piperidin-4-one and 4-chloroaniline.

Example D

1-(3,5-Bis-trifluoromethyl-benzoyl)-4-(3,4-dichloro-phenylamino)-piperidine-4-carbonitrile

The title compound, m.p. 195-197 °C and MS: $m/e = 512.1$ ($M+H^+$), was prepared in accordance with the general method of example B from 1-(3,5-bis-trifluoromethyl-benzoyl)-piperidin-4-one and 3,4-dichloroaniline.

Example E

1-(3,5-Bis-trifluoromethyl-benzoyl)-4-o-tolylamino-piperidine-4-carbonitrile

The title compound, m.p. 141-142 °C and MS: $m/e = 456.3$ ($M+H^+$), was prepared in accordance with the general method of example B from 1-(3,5-bis-trifluoromethyl-benzoyl)-piperidin-4-one and 2-methylaniline.

Example F

1-(3,5-Bis-trifluoromethyl-benzoyl)-4-(2-chloro-phenylamino)-piperidine-4-carbonitrile

The title compound, MS: $m/e = 474.1$ ($M-H^-$), was prepared in accordance with the general method of example B from 1-(3,5-bis-trifluoromethyl-benzoyl)-piperidin-4-one and 2-chloroaniline.

Example G

1-(3,5-Bis-trifluoromethyl-benzoyl)-4-(2-methoxy-phenylamino)-piperidine-4-carbonitrile

The title compound, MS: $m/e = 472.2$ ($M+H^+$), was prepared in accordance with the general method of example B from 1-(3,5-bis-trifluoromethyl-benzoyl)-piperidin-4-one and *o*-anisidine.

Example H

4-Benzylamino-1-(3,5-bis-trifluoromethyl-benzoyl)-piperidine-4-carbonitrile

The title compound, MS: $m/e = 456.3$ ($M+H^+$), was prepared in accordance with the general method of example B from 1-(3,5-bis-trifluoromethyl-benzoyl)-piperidin-4-one and benzylamine.

MS m/e (%): 586 ($M+H^+$, 100).

Example AA

Tablets of the following composition are manufactured in the usual manner:

	<u>mg/tablet</u>
Active substance	5
5 Lactose	45
Corn starch	15
Microcrystalline cellulose	34
Magnesium stearate	1
Tablet weight	100

10

Example BB

Capsules of the following composition are manufactured:

	<u>mg/capsule</u>
Active substance	10
15 Lactose	155
Corn starch	30
Talc	5
Capsule fill weight	200

20 The active substance, lactose and corn starch are firstly mixed in a mixer and then in a comminuting machine. The mixture is returned to the mixer, the talc is added thereto and mixed thoroughly. The mixture is filled by machine into hard gelatine capsules.

Example CC

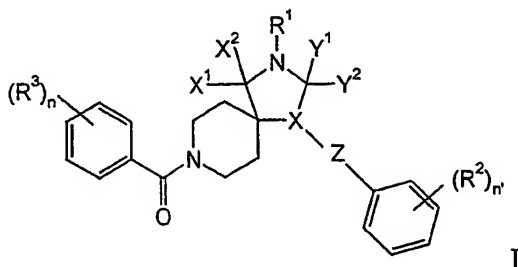
Suppositories of the following composition are manufactured:

	<u>mg/supp.</u>
Active substance	15
5 Suppository mass	1285
Total	1300

The suppository mass is melted in a glass or steel vessel, mixed thoroughly and cooled to 45°C. Thereupon, the finely powdered active substance is added thereto and stirred until it has dispersed completely. The mixture is poured into suppository moulds of
10 suitable size, left to cool, the suppositories are then removed from the moulds and packed individually in wax paper or metal foil.

Claims

1. Compounds of the general formula



5 wherein

R^1 is hydrogen, lower alkyl, lower alkenyl, phenyl or the following groups
 $-(CH_2)_m$ -non aromatic heterocyclyl, which is optionally substituted by lower
 alkyl, or is
 $-(CH_2)_m$ -heteroaryl, which is optionally substituted by one or two substituents
 10 selected from the group consisting of lower alkyl, lower alkoxy, halogen, CF_3 ,
 benzyl or cyano, or is
 $-(CH_2)_m-C(O)-NRR'$,
 $-(CH_2)_m-C(O)$ -lower alkyl,
 $-(CH_2)_m-C(O)-O$ -lower alkyl,
 15 $-(CH_2)_m-O$ -lower alkyl,
 $-(CH_2)_m-CH[C(O)-O$ -lower alkyl] $_2$,
 $-(CH_2)_mCH(OH)-CH_2-O$ -phenyl,
 $-(CH_2)_m-CH(CF_3)OH$,
 $-(CH_2)_m-OH$,
 20 $-(CH_2)_m-CN$,
 $-(CH_2)_m-NRR'$,
 $-(CH_2)_m$ -cycloalkyl or
 $-(CH_2)_m-CHF$;

R^2 is hydrogen, lower alkyl, halogen or lower alkoxy;

25 R^3 is lower alkyl, lower alkoxy, halogen or CF_3 ;

R, R' are the same or different and are hydrogen or lower alkyl;

X is $>N-$, $>C=$ or $>CH-$;

X^1/X^2 are independently from each other hydrogen, hydroxy or lower alkoxy or may be together an oxo group;

Y^1/Y^2 are independently from each other hydrogen, lower alkyl, $-(CH_2)_m$ -phenyl or may be together an oxo group;

5 Z is a bond, $-CH_2-$ or $-C(O)-$;

m is 0, 1, 2, 3 or 4;

n is 2 or 3;

n' 0, 1 or 2

and pharmaceutically acceptable acid addition salts thereof.

10 2. A compound according to claim 1, wherein R^3 is trifluoromethyl and n is 2.

3. A compound according to claims 1 and 2, in which X is $>N-$, X^1/X^2 are together an oxo group and Y^1/Y^2 are both hydrogen.

4. A compound according to claim 3, which is

8-(3,5-Bis-trifluoromethyl-benzoyl)-3-(4,6-dimethoxy-[1,3,5]triazin-2-yl)-1-phenyl-1,3,8-
15 triaza-spiro[4.5]decan-4-one,

8-(3,5-bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-3-(4,6-dimethoxy-[1,3,5]triazin-2-yl)-1,3,8-triaza-spiro[4.5]decan-4-one,

8-(3,5-bis-trifluoromethyl-benzoyl)-3-pyridin-3-ylmethyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one,

20 8-(3,5-bis-trifluoromethyl-benzoyl)-3-(2-isopropylamino-ethyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one,

8-(3,5-bis-trifluoromethyl-benzoyl)-3-(2-pyrrolidin-1-yl-ethyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one,

8-(3,5-bis-trifluoromethyl-benzoyl)-1-phenyl-3-pyridin-4-yl-1,3,8-triaza-spiro[4.5]decan-
25 4-one,

8-(3,5-bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-3-methyl-1,3,8-triaza-spiro[4.5]decan-4-one,

8-(3,5-bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-3-(3-dimethylamino-propyl)-
1,3,8-triaza-spiro[4.5]decan-4-one,

8-(3,5-bis-trifluoromethyl-benzoyl)-1-(2-chloro-phenyl)-3-pyridin-4-yl-1,3,8-triaza-
spiro[4.5]decan-4-one and

5 8-(3,5-bis-trifluoromethyl-benzoyl)-3-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-
one.

5. A compound according to claims 1 and 2, in which X is >N-, X¹/X² are together an
oxo group and one of Y¹/Y² is hydrogen and the other is different from hydrogen.

6. A compound according to claim 5, which is

10 (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-1-phenyl-1,3,8-triaza-
spiro[4.5]decan-4-one,

(rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-
4-one,

(rac)-2-benzyl-8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-
15 4-one,

(rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-phenyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-
4-one,

(rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-1-phenyl-3-pyridin-3-ylmethyl-1,3,8-
triaza-spiro[4.5]decan-4-one,

20 (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2,3-dimethyl-1-phenyl-1,3,8-triaza-
spiro[4.5]decan-4-one,

(rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-1-phenyl-3-(2-pyrrolidin-1-yl-ethyl)-
1,3,8-triaza-spiro[4.5]decan-4-one,

(rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-3-(3-dimethylamino-propyl)-2-methyl-1-
25 phenyl-1,3,8-triaza-spiro[4.5]decan-4-one,

(rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2,3-dimethyl-1-o-tolyl-1,3,8-triaza-
spiro[4.5]decan-4-one,

(rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-3-(2-piperazin-1-yl-ethyl)-1-o-tolyl-
1,3,8-triaza-spiro[4.5]decan-4-one,

(rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-3-(2-pyrrolidin-1-yl-ethyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one,

(rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-3-(2-piperidin-1-yl-ethyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one,

5 (rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-3-(2-methoxy-ethyl)-2-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one,

(rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-2-methyl-3-(2-morpholin-4-yl-ethyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one and

(rac)-8-(3,5-dichloro-benzoyl)-2-methyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decan-4-one.

10 7. A compound according to claims 1 and 2, wherein X is >N-, X¹/X² and Y¹/Y² are oxo groups.

8. A compound according to claim 7, which is

8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione,

8-(3,5-bis-trifluoromethyl-benzoyl)-3-pyridin-3-ylmethyl-1-o-tolyl-1,3,8-triaza-
15 spiro[4.5]decane-2,4-dione,

3-(1H-benzoimidazol-2-ylmethyl)-8-(3,5-bis-trifluoromethyl-benzoyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione,

8-(3,5-bis-trifluoromethyl-benzoyl)-3-(2-methyl-thiazol-4-ylmethyl)-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione,

20 8-(3,5-bis-trifluoromethyl-benzoyl)-3-furan-2-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione,

8-(3,5-bis-trifluoromethyl-benzoyl)-3-furan-2-ylmethyl-1-o-tolyl-1,3,8-triaza-spiro[4.5]decane-2,4-dione and

8-(3,5-bis-trifluoromethyl-benzoyl)-3-thiophen-2-ylmethyl-1-o-tolyl-1,3,8-triaza-
25 spiro[4.5]decane-2,4-dione.

9. A compound according to claims 1 and 2, wherein X is >C=.

10. A compound according to claim 9, which is

8-(3,5-bis-trifluoromethyl-benzoyl)-2-(2-pyrrolidin-1-yl-ethyl)-4-o-tolyl-2,8-diaza-spiro[4.5]dec-3-en-1-one and

8-(3,5-bis-trifluoromethyl-benzoyl)-2-(3-dimethylamino-propyl)-4-o-tolyl-2,8-diaza-spiro[4.5]dec-3-en-1-one.

5 11. A compound according to claims 1 and 2, wherein X is >CH-

12. A compound according to claim 11, which is

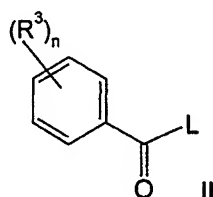
(rac)-8-(3,5-bis-trifluoromethyl-benzoyl)-4-o-tolyl-2,8-diaza-spiro[4.5]decan-1-one.

13. A medicament containing one or more compounds as claimed in any one of claims 1-12 and pharmaceutically acceptable excipients.

10 14. A medicament according to claim 13 for the treatment of diseases related to NK-1 receptor antagonists.

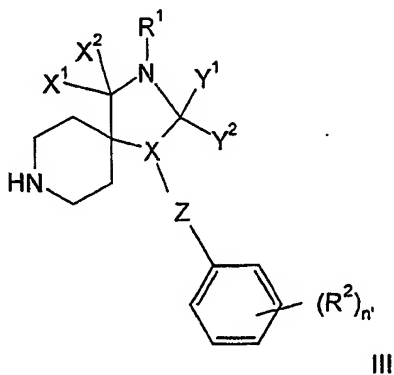
15. A process for preparing a compound of formula I as defined in claim 1, which process comprises

a) reacting a compound of formula



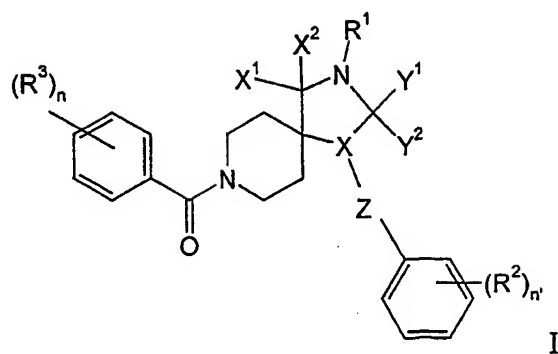
15

with a compound of formula



to a compound of formula

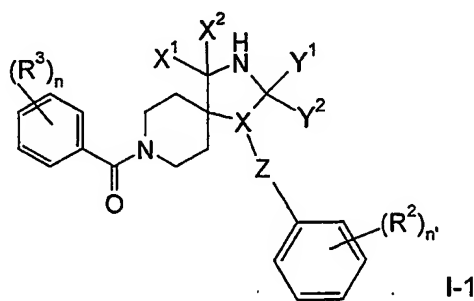
- 80 -



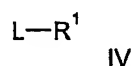
wherein L is a leaving group, for example halogen, such as chlorine, and the other substituents have the significances given above,

or

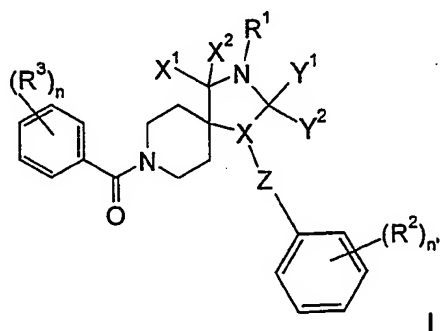
- 5 b) reacting a compound of formula



with a compound of formula

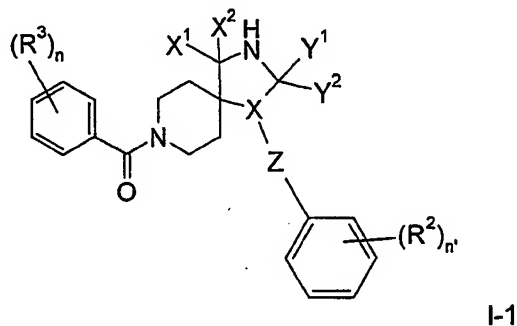


- 10 in the presence of sodium hydride or in the presence of potassium carbonate and CuCl,
 wherein in formula IV L is a leaving group, for example chlorine,
 to give a compound of formula

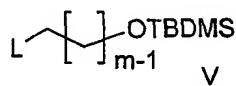


wherein the other substituents have the significances given above with the proviso that R^1 is not $-(CH_2)_m-OH$ and X^1/X^2 are not hydroxy, or

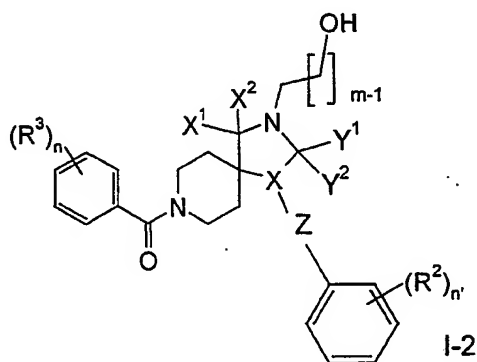
c) reacting a compound of formula



5 with a compound of formula



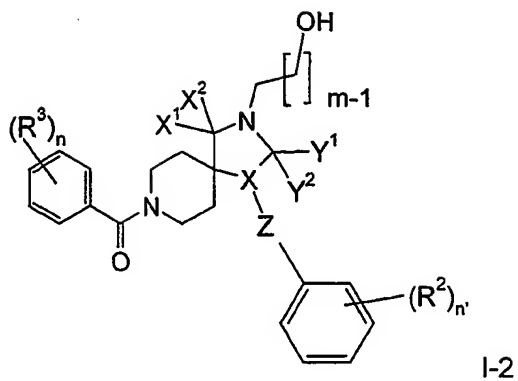
to a compound of formula



wherein TBDMS is a tert-butyldimethylsilyl group and the further definitions of
 10 substituents is given above, or

d) reacting a compound of formula

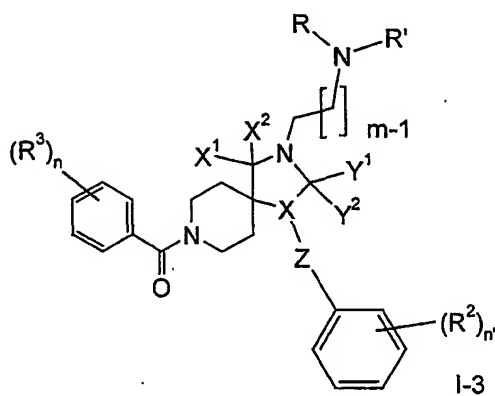
- 82 -



after activation as mesylate with a corresponding amine of formula



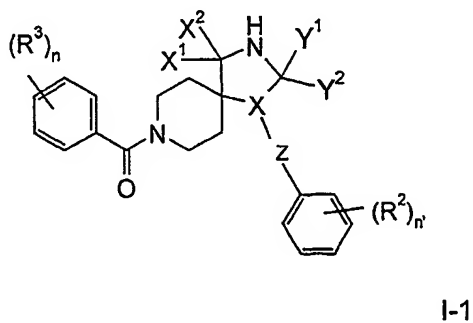
to give a compound of formula



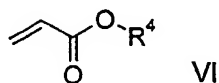
5

wherein the definitions of substituents are given above, or

e) reacting a compound of formula



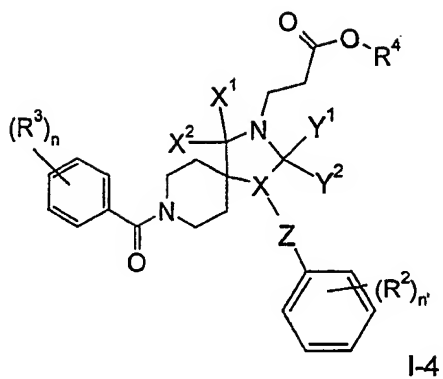
with a compound of formula



10

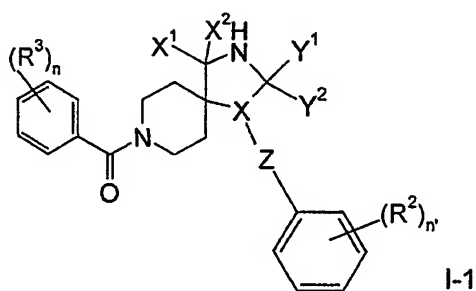
- 83 -

to a compound of formula

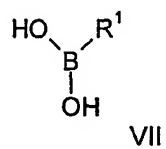


wherein R^4 is lower alkyl and the definitions of the other substituents are given above, or

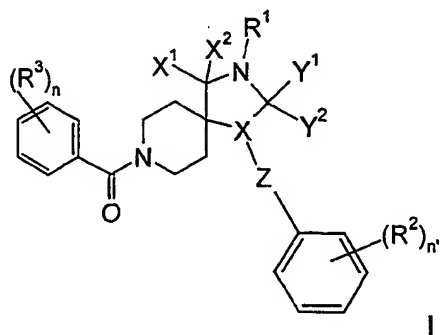
5 f) reacting a compound of formula



with a compound of formula



to a compound of formula

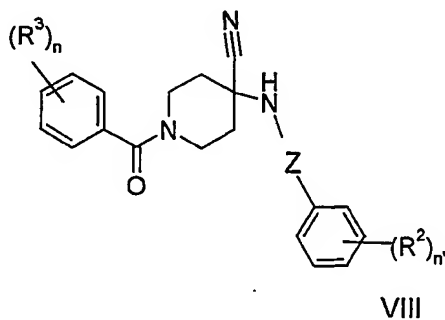


- 84 -

wherein R^1 is phenyl or heteroaryl, optionally substituted as described above and the definition of the remaining substituents is given above,

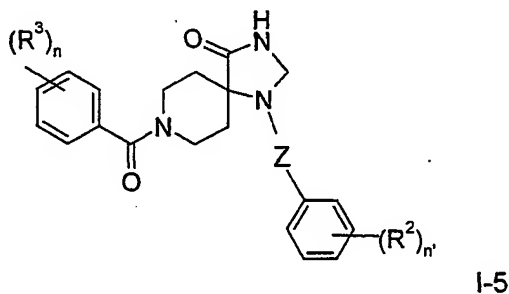
or

g) cyclizing a compound of formula



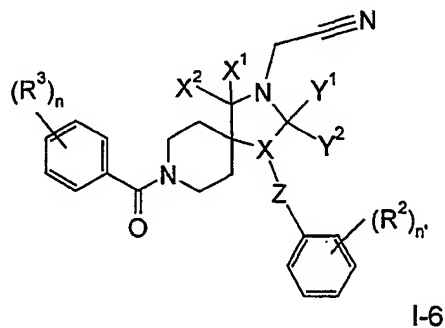
5

to a compound of formula



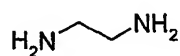
wherein the substituents are described above, or

h) reacting a compound of formula



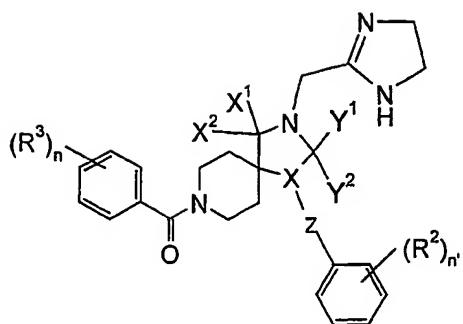
10

with



to give a compound of formula

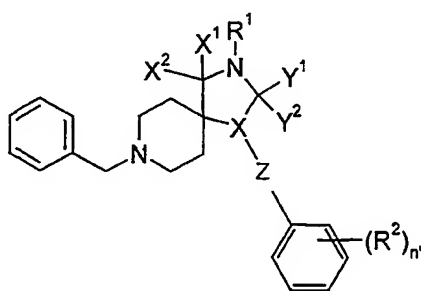
- 85 -



I-7

wherein the substituents are described above, or

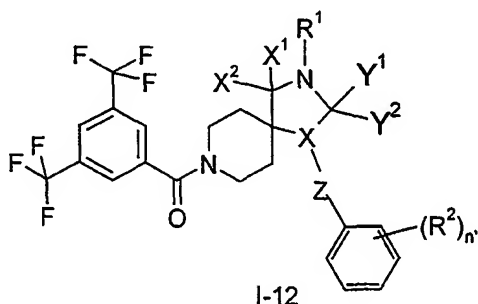
i) treating a compound of formula



XIV

5 with hydrogen on Pd/C and then with $(\text{CF}_3)_2\text{C}_6\text{H}_3\text{COCl}$

to obtain a compound of formula



I-12

wherein the substituents are given above, or

modifying one or more substituents R^1 - R^3 within the definitions given above, and

10 if desired, converting the compound obtained into a pharmaceutically acceptable acid addition salt.

- 86 -

16. A compound according to any one of claims 1-12, whenever prepared by a process as claimed in claim 15 or by an equivalent method.

17. The use of a compound in any one of claims 1-12 for the treatment of diseases.

18. The use of a compound in any one of claims 1-12 for the manufacture of
5 medicaments containing one or more compounds of formula I in accordance with claim 1 for the treatment of diseases related to NK-1 receptor antagonists.

19. The invention as hereinbefore described.

INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/EP 01/06305

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D471/10 A61K31/445 //(C07D471/10,239:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	M. C. DESAI, L. M. STEPHENS STRAMIELLO: "Polymer bound EDC (P-EDC): A convenient reagent for formation of an amide bond" TETRAHEDRON LETTERS, vol. 34, no. 48, 1993, pages 7685-7688, XP002068421 table 1	1
X	EP 0 623 589 A (PFIZER INC.) 9 November 1994 (1994-11-09) example 14	1
X	WO 97 11940 A (ELI LILLY AND CO.) 3 April 1997 (1997-04-03) claims 1,2	1

-/--



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

11 September 2001

Date of mailing of the international search report

18/09/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Herz, C

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/06305

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 25768 A (TREGA BIOSCINCES, INC.) 11 May 2000 (2000-05-11) claims 1-5 ---	1
A	WO 97 14686 A (ASTRA PHARMACEUTICALS LTD.) 24 April 1997 (1997-04-24) claims 1-18 ---	1-19
A	US 5 776 954 A (S. E. DE LASZLO ET AL.) 7 July 1998 (1998-07-07) claims 1-39 -----	1-19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 01/06305

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 623589	A	09-11-1994	US 5416193 A	16-05-1995
			AT 174901 T	15-01-1999
			DE 69415385 D	04-02-1999
			DE 69415385 T	12-05-1999
			DK 623589 T	23-08-1999
			ES 2124843 T	16-02-1999
			US 5616687 A	01-04-1997
WO 9711940	A	03-04-1997	AU 713235 B	25-11-1999
			AU 7382896 A	17-04-1997
			CA 2233204 A	03-04-1997
			EP 0854869 A	29-07-1998
			JP 11512723 T	02-11-1999
			NZ 320963 A	30-08-1999
WO 0025768	A	11-05-2000	AU 1455500 A	22-05-2000
			EP 1126833 A	29-08-2001
WO 9714686	A	24-04-1997	AU 704133 B	15-04-1999
			AU 7224396 A	07-05-1997
			BR 9610988 A	06-04-1999
			CZ 9801193 A	16-09-1998
			EE 9800116 A	15-10-1998
			EP 0858451 A	19-08-1998
			HU 9900028 A	28-04-1999
			JP 11513679 T	24-11-1999
			NO 981710 A	03-06-1998
			PL 326353 A	14-09-1998
			SK 45898 A	11-01-1999
			TR 9800697 T	21-07-1998
			US 5883102 A	16-03-1999
			ZA 9608767 A	17-04-1997
US 5776954	A	07-07-1998	NONE	